Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US05/006711

International filing date: 02 March 2005 (02.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/605,585
Filing date: 30 August 2004 (30.08.2004)

Date of receipt at the International Bureau: 25 April 2005 (25.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 18, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: ***60/605,585***
FILING DATE: ***August 30, 2004***
RELATED PCT APPLICATION NUMBER: ***PCT/US05/06711***

Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

3

"EXPRESS MAIL CERTIFICATE"

"Express Mail" Mailing Label Number EL964436067US

Date Of Deposit: August 30, 2004

I Hereby Certify That This Paper Or Fee Is Being Deposited With The United States Postal Service "Express Mail Post Office To Addressee" Service Under 37 CFR 1.10 On The Date Indicated Above And Is Addressed To: COMMISSIONER FOR PATENTS, MAIL STOP: PROVISIONAL APPLICATION, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450

Name Of Person Mailing Paper Or Fee

(Type Or Print) Lonnie Myers

Signature Lonnie Myers

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No. PU60768P3

INVENTOR(s) / APPLICANT(s) Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
YAMASHITA	Dennis	S.	Collegeville, Pennsylvania
LIN	Hong		Collegeville, Pennsylvania

TITLE OF THE INVENTION (280 characters max)

INHIBITORS OF AKT ACTIVITY

Correspondence Address:

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
709 Swedeland Road
King of Prussia

Telephone No. 610-270-5023
Facsimile No. 610-270-5090

State	PA	Zip Code	19406-0939	Country	United States of America

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	111	**Total Number of Pages = 112**
☒ Abstract	Number of Pages	1	
☐ Drawings	Number of Sheets		☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. **19-2570**	PROVISIONAL FILING FEE AMOUNT ($)	**$160.00**

Respectfully submitted,
Signature: Wayne J. Dustman Date: August 30, 2004
Wayne J. Dustman Registration No.: 33,870

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

SEND TO: Commissioner for Patents, P.O. Box 1450, Mail Stop: Provisional Application, Alexandria, VA 22313-1450.

20462
CUSTOMER NUMBER

N:\wjd\ptoltrs\pu60768p3trans.doc

INHIBITORS OF AKT ACTIVITY

FIELD OF THE INVENTION

This invention relates to novel pyridine compounds, the use of such compounds as inhibitors of protein kinase B (hereinafter PKB/Akt, PKB or Akt) activity and in the treatment of cancer and arthritis.

BACKGROUND OF THE INVENTION

The present invention relates to pyridine containing compounds that are inhibitors of the activity of one or more of the isoforms of the serine/threonine kinase, Akt (also known as protein kinase B). The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using the instant compounds in the treatment of cancer and arthritis (Liu et al. Current Opin. Pharmacology 3:317-22 (2003)).

Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Adams et al. *Science,* 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase -1 related proteinases, including caspase-3, caspase- 7, caspase-8 and caspase-9 etc (Thornberry et al. *Science,* 281:1312-1316 (1998)).

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997); Franke et al, *Cell,* 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science,* 275:628-630 (1997); Dudek et al., *Science,* 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P3), which in turn binds to, and promotes the activation of, the serine/ threonine kinase Akt, which contains a pleckstrin homology (PH)-domain (Franke et al *Cell,* 81:727-736 (1995); Hemmings *Science,* 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998),

Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or dominant negative Akt/PKB mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt/PKB by upstream kinases. In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed in breast and prostate cancer cell lines (Nakatani et al. *J. Biol.Chem.* 274:21528-21532 (1999). It was demonstrated that AKT2 was over-expressed in 12% of ovarian carcinomas and that amplification of AKT was especially frequent in 50% of undifferentiated tumors, suggestion that AKT may also be associated with tumor aggressiveness (Bellacosa, *et al., Int. J. Cancer*, 64, pp. 280-285, 1995). Increased Akt1 kinase activity has been reported in breast, ovarian and prostate cancers (Sun *et al. Am. J. Pathol. 159:* 431-7 (2001)).

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Nati. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

Three members of the Akt/PKB subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/ PKBα, Akt2/PKBβ, and Akt3/PKBγ respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akt/PKBs are activated by phosphorylation events occurring in response to PI3K signaling. PI3K phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidyl- inositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-

bisphosphate, which have been shown to bind to the PH domain of Akt/PKB. The current model of Akt/PKB activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt/PKB by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

Phosphorylation of Akt1/PKBα occurs on two regulatory sites, Thr^{308} in the catalytic domain activation loop and on Ser^{473} near the carboxy terminus (D. R. Alessi *et al. EMBO J.* 15:6541-6551 (1996) and R. Meier *et al. J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2/PKBβ and Akt3/PKBγ. The upstream kinase, which phosphorylates Akt/PKB at the activation loop site has been cloned and termed 3 '-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt/PKB, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt/PKB near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and wortmannin. However, PI3K inhibition has the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PdtIns(3,4,5)-P3, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. The compound UCN-01 is a reported inhibitor of PDK1. *Biochem. J.* 375(2):255 (2003). Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams et al. *Curr. Biol.* 10:439-448 (2000).

Small molecule inhibitors of AKT are useful in the treatment of tumors, especially those with activated AKT (e.g. PTEN null tumors and tumors with ras mutations). PTEN is a critical negative regulator of AKT and its function is lost in many cancers, including breast and prostate carcinomas, glioblastomas, and several cancer syndromes including Bannayan-Zonana syndrome (Maehama, T. *et al. Annual Review of Biochemistry, 70*: 247 (2001)), Cowden disease (Parsons, R.; Simpson, L. *Methods in Molecular Biology (Totowa, NJ, United States), 222 (Tumor Suppressor Genes, Volume 1)*: 147 (2003)), and Lhermitte-Duclos disease

(Backman, S. *et al. Current Opinion in Neurobiology, 12(5)*: 516 (2002)). AKT3 is up-regulated in estrogen receptor-deficient breast cancers and androgen-independent prostate cancer cell lines and AKT2 is over-expressed in pancreatic and ovarian carcinomas. Akt1 is amplified in gastric cancers (Staal, *Proc. Natl. Acad. Sci.* USA *84*: 5034-7 (1987) and upregulated in breast cancers (Stal *et al. Breast Cancer Res. 5*: R37-R44 (2003)). Therefore a small molecule AKT inhibitor is expected to be useful for the treatment of these types of cancer as well as other types of cancer. AKT inhibitors are also useful in combination with further chemotherapeutic agents.

It is an object of the instant invention to provide novel compounds that are inhibitors of Akt/PKB.

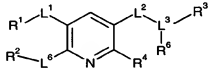
It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

It is also an object of the present invention to provide a method for treating cancer that comprises administering such inhibitors of Akt/PKB activity.

It is also an object of the present invention to provide a method for treating arthritis that comprises administering such inhibitors of Akt/PKB activity.

SUMMARY OF THE INVENTION

This invention relates to compounds of Formula (I):



(I)

wherein:

L^1 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

L^2 is selected from the group consisting of a bond, -O-, heterocycle, -N(R^5)-, -N(R^5)C(O)-, -S-, -S(O)-, -S(O_2)-, and -C(O)N(R^5)-;

L^3 is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, methylamino, dimethylamino, oxo, and hydroxy;

L^6 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

R^1 is selected from the group consisting of aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocycle and substituted heterocycle;

R^2 is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, C_1-C_{12}aryl, aryloxy, substituted C_1-C_{12}aryloxy, -O(CH_2)$_q$$R^{31}$, -NHC(O)-NH$R^{41}$, -C(O)$R^{43}$, substituted cycloalkyl, substituted C_1-C_{12}aryl, heterocycle, substituted heterocycle, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR^7, -C(O)NR^8R^9, -S(O_2)NR^8R^9, and -S(O)$_n$$R^7$,

where n is 0-2, q is 1-6,

R^7 is hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl,

R^{31} is C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, acyloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{41} is selected from hydrogen, C_1-C_{12}aryl, cycloalkyl and heterocycle, wherein C_1-C_{12}aryl, cycloalkyl and heterocycle are optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{43} is selected from C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from:

halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl, and R^8 and R^9 are independently hydrogen, cycloalkyl, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR^{10}, -S(O)$_n$$R^{10}$, -C(O)N$R^{10}$$R^{11}$, -S(O)$_2NR^{10}$$R^{11}$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, and substituted aryl, or R^8 and R^9 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^{10} and R^{11} are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2,

and when L^6 is a bond, R^2 can additionally be halogen;

R^3 and R^6 are independently selected from the group consisting of hydrogen, amino, methylamino, dimethylamino, aryl, substituted aryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, -S-C_1-C_{12}aryl, -O-C_1-C_{12}aryl, -OalkylC$_1$-C_{12}aryl, aryloxy, substituted aryloxy and arylalkoxy; and

R^4 is selected from the group consisting of hydrogen and halogen;

where R^5 is selected from the group consisting of hydrogen, -S(O)$_2$CH$_3$, -S(O)$_2$H and alkyl;

and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

This invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

This invention relates to a method of treating arthritis, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of Akt/PKB.

In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented Akt/PKB inhibiting compounds.

Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

Also included in the present invention are methods of co-administering the presently invented Akt/PKB inhibiting compounds with further active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of Formula (I) as described above.

The presently invented compounds of Formula (I) inhibit Akt/PKB activity. In particular, the compounds disclosed herein inhibit each of the three Akt/PKB isoforms.

Included among the presently invented compounds of Formula (I) are those having Formula (I):
wherein

L^1 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

L^2 is selected from the group consisting of a bond, -O-, heterocycle, -N(R^5)-, -N(R^5)C(O)-, -S-, -S(O)-, -S(O_2)-, and -C(O)N(R^5)-;

L^3 is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, methylamino, dimethylamino, oxo, and hydroxy;

L^6 is a bond;

R^1 is selected from the group consisting of C_1-C_{12}aryl and substituted C_1-C_{12}aryl;

R^2 is selected from alkyl, substituted alkyl, halogen, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, and C_1-C_{12}aryl optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, C_1-C_{12}aryl, C_1-C_{12}aryloxy, $-O(CH_2)_qR^{31}$, $-NHC(O)-NHR^{41}$, $-C(O)R^{43}$, hydroxy, alkoxy, cycloalkyl, N-acylamino, nitro and halogen,

where q is 1-6,

R^{31} is C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, acyloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{41} is selected from hydrogen, C_1-C_{12}aryl, cycloalkyl and heterocycle, wherein C_1-C_{12}aryl, cycloalkyl and heterocycle are optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{43} is selected from C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxyl, nitro, tetrazole, cyano, oxo and trifluoromethyl,

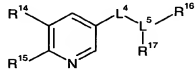
R^3 and R^6 are independently selected from the group consisting of hydrogen, amino, methylamino, dimethylamino, aryl, substituted aryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, $-S-C_1$-C_{12}aryl, aryloxy and arylalkoxy; and

R^4 is selected from the group consisting of hydrogen and halogen;

where R^5 is selected from the group consisting of hydrogen, $-S(O)_2CH_3$, $-S(O)_2H$ and alkyl;

and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

Included among the presently invented compounds of Formula (I) are those having Formula (II):



(II)

wherein:

L^4 is selected from the group consisting of a bond, heterocycle, and -O-;

L^5 is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from the group consisting of C_1-C_{12}aryl, and substituted C_1-C_{12}aryl;

R^{15} is selected from alkyl, substituted alkyl, halogen, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, C_1-C_{12}aryl and C_1-C_{12}aryl optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, aryloxy, $-O(CH_2)_qR^{31}$, -NHC(O)-NHR^{41}, -C(O)R^{43}, hydroxy, alkoxy, acyloxy, amino, cycloalkyl, N-acylamino, nitro, cyano and halogen,

where q is 1-6,

R^{31} is C_1-C_{12}aryl optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, and hydroxy,

R^{41} is selected from hydrogen and C_1-C_{12}aryl optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, and hydroxy,

R^{43} is C_1-C_{12}aryl substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, and hydroxy,

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{12}aryl, substituted C_1-C_{12}aryl, heterocycle, cycloalkyl, -S-C_1-C_{12}aryl, and C_1-C_{12}arylalkoxy; and

and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

Included among the presently invented compounds of Formula (II) are those in which:

L^4 is selected from the group consisting of a bond, and -O-;

L^5 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from the group consisting of C_1-C_{12}aryl, and substituted C_1-C_{12}aryl;

R^{15} is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{12}aryl and substituted C_1-C_{12}aryl;

and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

Included among the presently invented compounds of Formula (II) are those in which:

L^4 is selected from the group consisting of a bond, heterocycle, and -O-;

L^5 is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from the group consisting of C_1-C_{12}aryl, and substituted C_1-C_{12}aryl;

R^{15} is selected from alkyl, substituted alkyl, halogen, cycloalkyl, and C_1-C_{12}aryl optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, C_1-C_{12}aryloxy, $-O(CH_2)_qR^{31}$, $-NHC(O)-NHR^{41}$, $-C(O)R^{43}$, hydroxy, alkoxy, cycloalkyl, N-acylamino, nitro and halogen,

where q is 1-6,

R^{31} is C_1-C_{12}aryl optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, and hydroxy,

R^{41} is selected from hydrogen and C_1-C_{12}aryl optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, and hydroxy,

R^{43} is C_1-C_{12}aryl substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, and hydroxy,

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{12}aryl, substituted C_1-C_{12}aryl, heterocycle, cycloalkyl, $-S-C_1$-C_{12}aryl, and C_1-C_{12}arylalkoxy; and

and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

Included among the presently invented compounds of Formula (II) are those in which:

L^4 is selected from the group consisting of a bond, and -O-;

L^5 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from phenyl, pyridine, indazole, 7-azaindole, quinoline, isoquinoline, substituted phenyl, substituted pyridine, substituted indazole, substituted 7-azaindole, substituted quinoline and substituted isoquinoline;

R^{15} is selected from cycloalkyl, substituted cycloalkyl, phenyl, pyridine, thiophene, furan, pyrrole, indazole, quinoline, isoquinoline, 7-azaindole, substituted phenyl, substituted pyridine, substituted thiophene, substituted

furan, substituted indazole, substituted quinoline, substituted 7-azaindole and substituted isoquinoline; and

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, phenyl, pyridine, thiophene, furan, pyrrole, substituted phenyl, substituted pyridine, substituted thiophene, substituted furan, and substituted pyrrole;

and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

Included among the presently invented compounds of Formula (II) are those having Formula (II):
wherein

L^4 is selected from the group consisting of a bond, and -O-;

L^5 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from the group consisting of C_1-C_{12}aryl, and substituted C_1-C_{12}aryl;

R^{15} is selected from cycloalkyl and substituted cycloalkyl; and

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{12}aryl and substituted C_1-C_{12}aryl;

and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

Included among the compounds useful in the present invention are:

(S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-furan-2-yl-5-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[5,6-bis-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-thiophen-2yl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-(4-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-(3-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-benzyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclopent-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclopentyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclohex-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclohexyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

3-Methyl-5-[2-phenyl-5-(piperidin-4-ylmethoxy)-pyridin-3-yl]-1H-indazole;

3-[5-(3-Methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-propylamine;

(S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-thiophen-2-yl)-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-furan-2-yl)-pyridin-3-yloxy]-ethylamine;

3-Methyl-5-[2-phenyl-5-(4-pyridin-3-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole;

3-Methyl-5-[2-phenyl-5-(4-pyridin-4-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole;

[(1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(5-chloro-2-thienyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(3-aminophenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

(S)-1-Benzyl-2-[5-(1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-{6-[3-(3-fluoro-benzyloxy)phenyl]-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy}-ethylamine;

(S)-1-Benzyl-2-[5-(3-phenyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

N-{3-[5-{[(2S)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}benzamide;

N-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}-2,6-difluorobenzamide;

N-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}cyclohexanecarboxamide;

[(1*S*)-2-({5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(2-thienyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine;

[(1*S*)-2-({5-[3-(3-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(3-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

[(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(2-thienyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine;

[(1*S*)-2-({5-[3-(3-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(3-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

[(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1-methyl-1*H*-pyrazol-4-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(1-[(3-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

((1*S*)-2-phenyl-1-{[(6-phenyl-5-{3-[5-(1-piperazinylmethyl)-2-furanyl]-1*H*-indazol-5-yl}-3-pyridinyl)oxy]methyl}ethyl)amine;

[(1*S*)-2-({6-(3-furanyl)-5-[3-(2-furanyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-(3-methyl-1*H*-indazol-5-yl)-6-[3-(phenyloxy)phenyl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

3-[({5-[5-([(2*S*)-2-amino-3-phenylpropyl]oxy}-2-phenyl-3-pyridinyl)-1*H*-indazol-3-yl]-2-furanyl}methyl)amino]propanenitrile;

[(1*S*)-2-({6-(2-furanyl)-5-[3-(2-furanyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

{5-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]-2-thienyl}methanol;

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(phenylmethyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1-methyl-1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

5-(5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-2-phenyl-3-pyridinyl)-1*H*-indazol-3-amine;

[(1*S*)-2-({5-[3-(1-methylethenyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrazol-4-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

(2*S*)-*N*,*N*-dimethyl-1-{[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-3-phenyl-2-propanamine;

[(1*S*)-2-{[3-(3-methyl-1*H*-indazol-5-yl)-2,4'-bipyridin-5-yl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[3-(3-methyl-1*H*-indazol-5-yl)-2,3'-bipyridin-5-yl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-iodo-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-[(5-(3-methyl-1*H*-indazol-5-yl)-6-{3-[(trifluoromethyl)oxy]phenyl}-3-pyridinyl)oxy]-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(3,5-dimethyl-4-isoxazolyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

4-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

2-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

[(1*S*)-2-{[6-[3-(ethyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-(3-methyl-1*H*-indazol-5-yl)-6-[3-(methyloxy)phenyl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}(phenyl)methanone;

[(1*S*)-2-{[6-{3-[(1-methylethyl)oxy]phenyl}-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(2-{[(3-fluorophenyl)methyl]oxy}phenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(4-{[(3-fluorophenyl)methyl]oxy}phenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(5-chloro-2-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(4-methyl-2-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(5-methyl-2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(5-methyl-2-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-ethenyl-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(1*H*-pyrrol-2-yl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine;

[(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}methyl)ethyl]amine;

5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-*N*-(3-phenylpropyl)-3-pyridinamine;

5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-*N*-(3-phenylbutyl)-3-pyridinamine;

[(2*S*)-2-amino-3-phenylpropyl][5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine;

[(2*S*)-2-amino-3-phenylpropyl][6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]amine;

((1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-{[(phenylmethyl)oxy]methyl}ethyl)amine;

N-[(2*S*)-2-amino-3-phenylpropyl]-*N*-[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]methanesulfonamide;

5-(3-methyl-1*H*-indazol-5-yl)-*N*-[2-methyl-2-(phenylthio)propyl]-6-phenyl-3-pyridinamine;

[(1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(1*H*-indol-3-ylmethyl)ethyl]amine;

((1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-{[(phenylmethyl)oxy]methyl}ethyl)amine;

(2*S*)-2-amino-3-{[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-propanol;

5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-*N*-[(2*S*)-2-pyrrolidinylmethyl]-3-pyridinamine;

((2*S*)-2-amino-3-{4-[(phenylmethyl)oxy]phenyl}propyl)[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine;

[(2*S*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine;

[(2*S*)-2-amino-3-phenylpropyl][6-(3-furanyl)-5-(1*H*-indazol-5-yl)-3-pyridinyl]amine;

[(2*S*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-(3-thienyl)-3-pyridinyl]amine;

2-[5-[[(2*S*)-2-amino-3-phenylpropyl]amino}-3-(1*H*-indazol-5-yl)-2-pyridinyl]phenol;

2-[5-{[(2*S*)-2-amino-3-phenylpropyl]amino}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

[(2*S*)-2-amino-3-phenylpropyl][5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]amine;

[(2*S*)-2-amino-3-phenylpropyl][5-(3-methyl-1*H*-indazol-5-yl)-6-(5-methyl-2-thienyl)-3-pyridinyl]amine;

[(2*R*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-(3-thienyl)-3-pyridinyl]amine;

2-[5-[[(2*S*)-2-amino-3-(1*H*-indol-3-yl)propyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

[(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}methyl)ethyl]amine;

[(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-(5-methyl-2-thienyl)-3-pyridinyl]oxy}methyl)ethyl]amine;

[(1*S*)-2-{[6-ethyl-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(3-furanyl)-5-(1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-ethenyl-1*H*-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-ethyl-1*H*-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({6-(3-furanyl)-5-[3-(3-pyridinyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-methyl-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-(3-methyl-1*H*-indazol-5-yl)-6-[2-(methyloxy)phenyl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-[2-(ethyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-[5-chloro-2-(methyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-[5-fluoro-2-(propyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(1-methylethyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine; and

[(1*S*)-2-{[5-(6-fluoro-3-methyl-1*H*-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention.

By the term "aryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 1 to 14 carbon atoms and optionally containing from one to five heteroatoms, provided that when the number of carbon atoms is 1 the aromatic ring contains at least four heteroatoms, when the number of carbon atoms is 2 the aromatic ring contains at least three heteroatoms, when the number of carbons is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom.

By the term "C_1-C_{12}aryl" as used herein, unless otherwise defined, is meant phenyl, naphthalene, 3,4-methylenedioxyphenyl, pyridine, biphenyl, indazole, quinoline, isoquinoline, 7-azaindole, pyrimidine, quinazoline, thiophene, furan, pyrrole, pyrazole, imidazole, benzothiophene, benzofuran, isoxazole, indole and tetrazole.

The term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has one or more substituents selected from the group consisting of: -CO_2R^{20}, C_1-C_{12}aryl, C_1-C_{12}arylamino, C_1-C_{12}arylalkyl, cycloalkyl, heterocyclealkylC_1-C_{12}aryl, cyanoalkylaminoalkylC_1-C_{12}aryl, -$C(O)NHS(O)_2R^{20}$, -$NHS(O)_2R^{20}$, -$NHC(O)$-NHR^{41}, hydroxyalkyl, alkoxy, -$C(O)NR^{21}R^{22}$, acyloxy, alkyl, R^{42}, -NR^{42}, -$C(O)R^{43}$, C_1-C_{12}aryloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, -$(CH_2)_gC(O)OR^{23}$, -$S(O)_nR^{23}$, -$O(CH_2)_qR^{31}$, -$O(CH_2)_yCH(R^{31})(CH_2)_z(CH_3)$, nitro, tetrazole, cyano, oxo, halogen, trifluoromethoxy, trifluoroalkoxy and trifluoromethyl;
where
n is 0-2, g is 0-6, q is 1-6, y is 0-6, z is 0-6,

R^{41} is selected from hydrogen, C_1-C_{12}aryl, cycloalkyl and heterocycle, wherein C_1-C_{12}aryl, cycloalkyl and heterocycle are optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{42} is selected from C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{43} is selected from C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxyl, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{31} is C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, acyloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{23} is hydrogen or alkyl,

R^{20} is selected form hydrogen, C_1-C_4alkyl, aryl and trifluoromethyl, and

R^{21} and R^{22} are independently selected form hydrogen, C_1-C_4alkyl, aryl and trifluoromethyl.

By the term "alkoxy" as used herein is meant -Oalkyl where alkyl is as described herein including $-OCH_3$ and $-OC(CH_3)_2CH_3$.

The term "cycloalkyl" as used herein unless otherwise defined, is meant a nonaromatic, unsaturated or saturated, cyclic or polycyclic C_3-C_{12}.

Examples of cycloalkyl and substituted cycloalkyl substituents as used herein include: cyclohexyl, 4-hydroxy-cyclohexyl, 2-ethylcyclohexyl, cyclohexene, propyl 4-methoxycyclohexyl, 4-methoxycyclohexyl, 4-carboxycyclohexyl, cyclopropyl, cyclopentene and cyclopentyl.

The term "heterocycle," as used herein, unless otherwise defined, is meant a cyclic or polycyclic, non-aromatic, three-, four-, five-, six-, or seven-membered ring containing at least one atom, selected from the group consisting of oxygen, nitrogen, and sulfur. The five-membered rings have zero or one double bond and the six- and seven-membered rings have zero, one, or two double bonds.

Examples of heterocyclic groups as used herein include: dihydroisoindolyl, dihydroisoquinolinyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-

dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl.

By the term "acyloxy" as used herein is meant -OC(O)alkyl where alkyl is as described herein. Examples of acyloxy substituents as used herein include: -$OC(O)CH_3$, -$OC(O)CH(CH_3)_2$ and -$OC(O)(CH_2)_3CH_3$.

By the term "N-acylamino" as used herein is meant a substituent selected from: -N(H)C(O)alkyl, -N(H)C(O)cycloalkyl and -N(H)C(O)aryl; where alkyl and cycloalkyl are as described herein and aryl is C_1-C_{12}aryl as described herein and where the alkyl, cycloalkyl, and aryl are optionally substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl. Examples of N-acylamino substituents as used herein include: -N(H)C(O)CH_3, -N(H)C(O)$CH(CH_3)_2$ and -N(H)C(O)$(CH_2)_3CH_3$.

By the term "aryloxy" as used herein is meant -Oaryl where aryl is phenyl, naphthyl, 3,4-methylenedioxyphenyl, pyridyl or biphenyl optionally substituted with one or more substituents selected from the group consisting of: alkyl, hydroxyalkyl, alkoxy, trifuloromethyl, acyloxy, amino, N-acylamino, hydroxy, -$(CH_2)_gC(O)OR^{25}$, -$S(O)_nR^{25}$, nitro, cyano, halogen and protected -OH, where g is 0-6, R^{25} is hydrogen or alkyl, and n is 0-2. Examples of aryloxy substituents as used herein include: phenoxy, 4-fluorophenyloxy and biphenyloxy.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein is meant a linear or branched, saturated or unsaturated hydrocarbon chain, and unless otherwise defined, the carbon chain will contain from 1 to 12 carbon atoms. Examples of alkyl and substituted alkyl substituents as used herein include: -CH_3, -CH_2-CH_3, -CH_2-CH_2-CH_3, -$CH(CH_3)_2$, -CH_2-CH_2-$C(CH_3)_3$, -CH_2-CF_3, -C≡C-$C(CH_3)_3$, -C≡C-CH_2-OH, cyclopropylmethyl, phenylmethyl, -CH_2-$C(CH_3)_2$-CH_2-NH_2, -CH_2-$C(CH_3)_2$-, -C≡C-C_6H_5, -C≡C-$C(CH_3)_2$-OH, -CH_2-CH(OH)-CH(OH)-CH(OH)-CH(OH)-CH_2-OH, piperidinylmethyl, methoxyphenylethyl, -$C(CH_3)_3$, -$(CH_2)_3$-CH_3, -CH_2-$CH(CH_3)_2$, -$CH(CH_3)$-CH_2-CH_3, -CH=CH_2, and -C≡C-CH_3.

By the term "treating" and derivatives thereof as used herein, is meant prophylatic and therapeutic therapy.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

As used herein, the term "effective amount" and derivatives thereof means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" and derivatives thereof means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, pivaloyloxymethyl, and the like for -COOH, and acetate maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics, for use as sustained release or prodrug formulations.

The novel compounds of Formulas I and II are prepared as shown in Schemes 1 through 7 below, or by analogous methods, wherein the 'L' and 'R' substituents are as defined in Formulas I and II respectively and provided that the 'L' and 'R' substituents do not include any such substituents that render inoperative the processes of Schemes 1 through 7. All of the starting materials are commercially available or are readily made from commercially available starting materials by those of skill in the art.

Ethers such as **1(b)** can be prepared by Mitsunobu coupling with hydroxy-pyridines such as 2-chloro-3-bromo-5-hydroxy-pyridine and alcohols such as N-Boc-(2*S*)-2-amino-3-phenyl-1-propanol (Scheme **1**) or Boc-(2S)-2-amino-3-(3-indole)-1-propanol (Scheme 10). An aryl moiety such as a 6-(3-methyl-indazole) can be selectively introduced by stoichiometric use of the Suzuki reaction (Pd-mediated cross coupling between aryl boronic acids or aryl boronic esters and aryl halides or triflates) or a Stille reaction (Pd-mediated cross coupling between aryltrialkylstannanes and aryl halides or triflates) to produce intermediates such as **1(d)** (Scheme 1). A second aryl moiety such as a phenyl group can be introduced at the adjacent position on the pyridine by a second Suzuki or Stille reaction

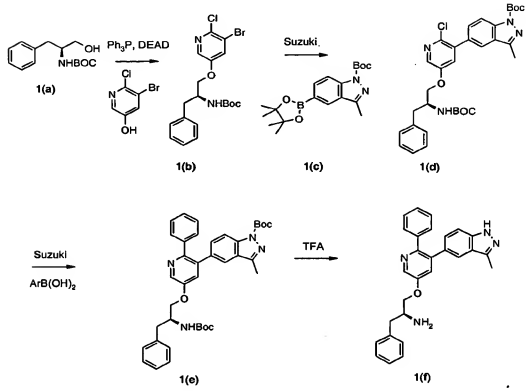
forming trisubstituted pyridines such as **1(e)** (Scheme 1). Alternatively, an alkyl or substituted alkyl group such as a benzyl moiety can be introduced by Pd-mediated coupling with an organometallic reagent such as benzyl zinc bromide (Scheme 2) to produce intermediates such as **7(a)**. Alternatively, the Pd-mediated cross coupling steps may precede the etherification or Mitsunobu reaction steps as shown in Scheme 3. Another variant on the synthesis is to introduce alternative linker groups such as amines in place of ethers as exemplified in Scheme 4. For example, ipso-addition of an amine such as 1-(3-pyridinylmethyl)piperazine to a pyridine trifluoromethylsulfonate (triflate or TfO) intermediate such as **16(a)** and elimination under microwave conditions in a solvent such as N-methyl2-pyrollidone (NMP) produces amine analogs such as **16(b)**. In addition, the aryl groups on the substituted pyridine may be further functionalized by further reactions such as acylation of a intermediate amines such as **25(b)** to form amides such **25(c)** as shown in Scheme 5. Final deprotection steps such removal of t-butyloxycarbonyl (Boc) groups with trifluoroacetic acid (TFA) or a solution of hydrochloric acid (HCl) or removal of a carbobenzyloxy (Cbz) by hydrogenolysis with heterogeneous metals such as Pd on carbon or with a solution of hydrogen bromide (HBr) produces the desired final products such as **1(f)** (Scheme 1), **7(b)** (Scheme 2), **12(d)** (Scheme 3), or **25(d)** (Scheme 5). 3-substituted indazole analogs can be prepared by selective iodination of the parent indazole and Pd-mediated cross coupling steps (Scheme 6). Also, *N*-alkylated analogs of the indazole such as **33(d)** can be prepared by treating intermediate indazoles such as **16(a)** with electrophilic reagents such as Meerwein's reagent followed by a Mitsunobu reaction as described above (Scheme 7). Indazoles may be further substituted by iodinating the 3-position using an iodinating reagent such as iodine and a base such as potassium hydroxide followed by a Pd-mediated cross coupling step such as Suzuki, Stille, Buchwald, or Negishi reactions (Schemes 8 and 9), followed by deprotection steps.

Amines such as 75(b) can be prepared by reductive amination using aldehydes such as 3-phenyl-propanal and a reducing agent such as triacetoxyborohydride (Scheme 11). The amine may be further functionalized with sulfonylating agents such as methylsulfonyl chloride (Scheme 12).

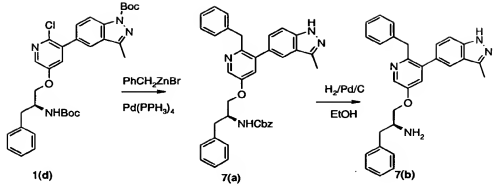
Amines such as 82(c) may also be prepared by reductive amination between amines such as 2-chloro-3-bromo-5-amino-pyridine and aldehydes such as 1,1-dimethylethyl [(1*S*)-1-formyl-2-(1*H*-indol-3-yl)ethyl]carbamate with reducing agents such as sodium triacetoxyborohydride or sodium borohydride, followed by Pd-mediated cross coupling reactions using the methods of Suzuki, Stille,

Buchwald, or Negishi, and final deprotection steps such as Boc removal with trifluoroacetic acid or HCl (Scheme 13).

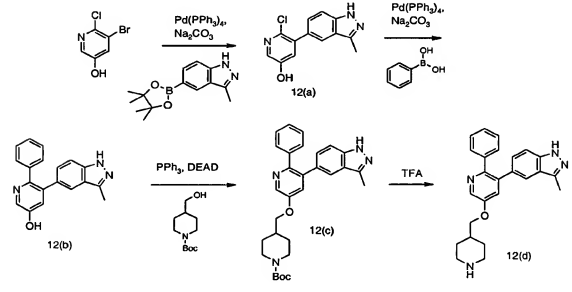
SCHEME 1



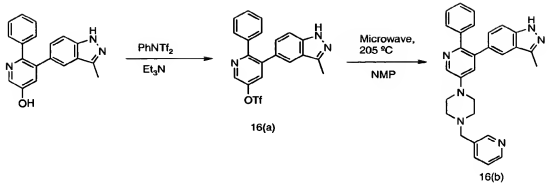
SCHEME 2



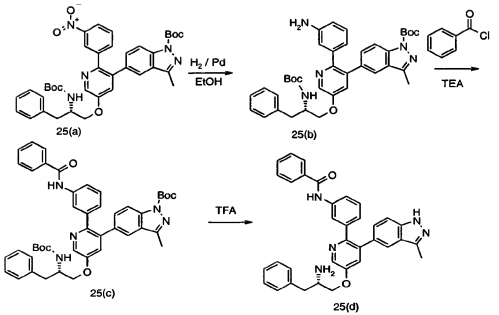
SCHEME 3



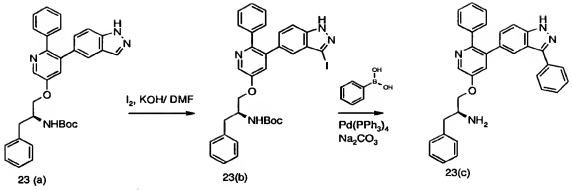
SCHEME 4



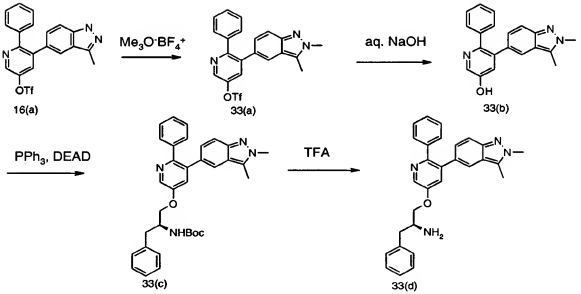
SCHEME 5



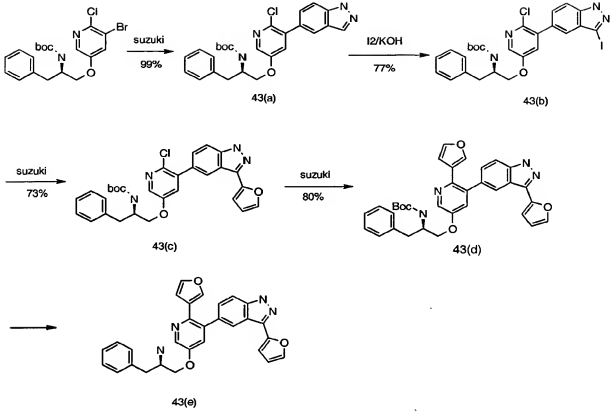
SCHEME 6



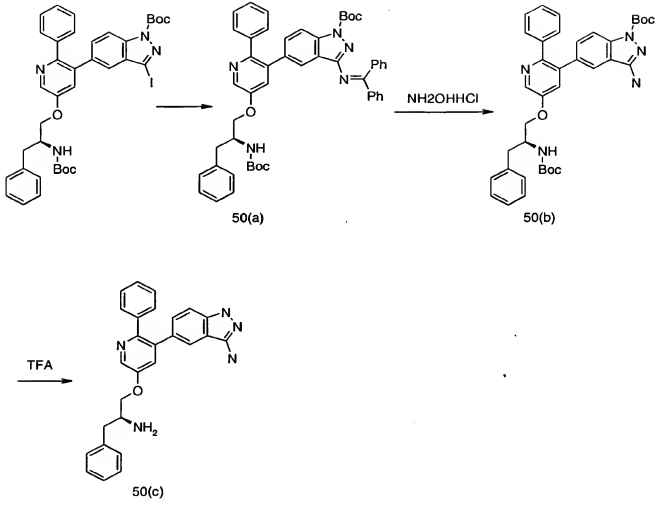
SCHEME 7



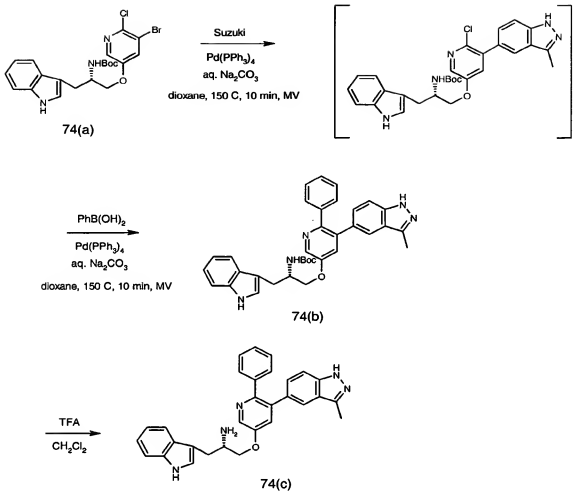
SCHEME 8


boc
Cl
Br
suzuki
99%
43(a)
I2/KOH
77%
43(b)
suzuki
73%
43(c)
suzuki
80%
Boc
43(d)
43(e)

SCHEME 9

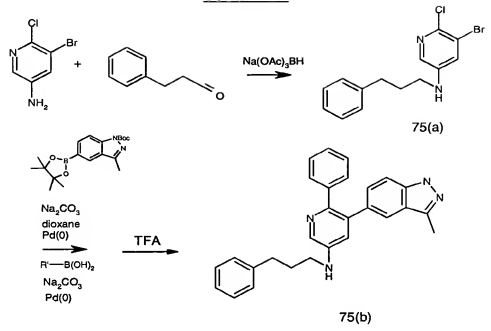


SCHEME 10


Cl
Br
N
NHBoc
O
H
N
74(a)
Suzuki
Pd(PPh3)4
aq. Na2CO3
dioxane, 150 C, 10 min, MV
PhB(OH)2
Pd(PPh3)4
aq. Na2CO3
dioxane, 150 C, 10 min, MV
74(b)
TFA
CH2Cl2
NH2
74(c)

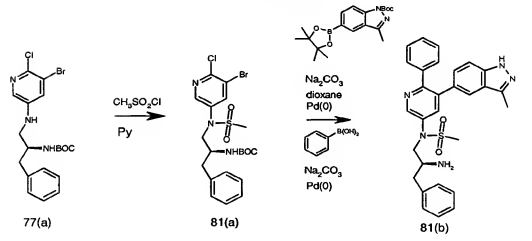
5

SCHEME 11



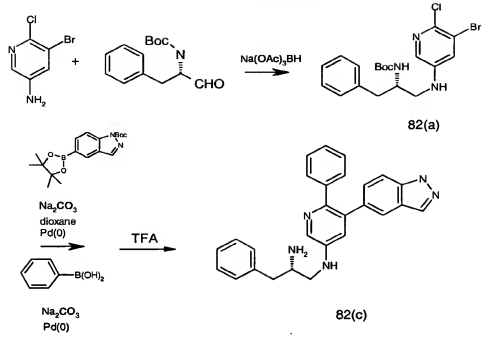
5

SCHEME 12



10

SCHEME 13



By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of an AKT inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment, or to be useful in the treatment of arthritis. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer or arthritis. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Typically, any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be co-administered in the treatment of cancer in the present invention. Examples of such agents can be found in Cancer Principles and Practice f Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved.

Typical anti-neoplastic agents useful in the present invention include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

Examples of a further active ingredient or ingredients for use in combination with the presently invented AKT inhibiting compounds are chemotherapeutic agents.

Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

Diterpenoids, which are derived from natural sources, are phase specific anti -cancer agents that operate at the G_2/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β-tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.

Paclitaxel, 5β,20-epoxy-1,2α,4,7β,10β,13α-hexa-hydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine; is a natural diterpene product isolated from the Pacific yew tree *Taxus brevifolia* and is commercially available as an injectable solution TAXOL®. It is a member of the taxane family of terpenes. It was first isolated in 1971 by Wani et al. J. Am. Chem, Soc., 93:2325. 1971), who characterized its structure by chemical and X-ray crystallographic methods. One mechanism for its activity relates to paclitaxel's capacity to bind tubulin, thereby inhibiting cancer cell growth. Schiff et al., Proc. Natl, Acad, Sci. USA, 77:1561-1565 (1980); Schiff et al., Nature, 277:665-667 (1979); Kumar, J. Biol, Chem, 256: 10435-10441 (1981). For a review of synthesis and anticancer activity of some paclitaxel derivatives see: D. G. I. Kingston *et al.*, Studies in Organic Chemistry vol. 26, entitled "New trends in Natural Products Chemistry 1986", Attaur-Rahman, P.W. Le Quesne, Eds. (Elsevier, Amsterdam, 1986) pp 219-235.

Paclitaxel has been approved for clinical use in the treatment of refractory ovarian cancer in the United States (Markman et al., Yale Journal of Biology and Medicine, 64:583, 1991; McGuire et al., Ann. Intern, Med., 111:273, 1989) and for the treatment of breast cancer (Holmes et al., J. Nat. Cancer Inst., 83:1797, 1991.) It is a potential candidate for treatment of neoplasms in the skin (Einzig et. al., Proc. Am. Soc. Clin. Oncol., 20:46) and head and neck carcinomas (Forastire et. al., Sem. Oncol., 20:56, 1990). The compound also shows potential for the treatment of polycystic kidney disease (Woo et. al., Nature, 368:750. 1994), lung cancer and malaria. Treatment of patients with paclitaxel results in bone marrow suppression (multiple cell lineages, Ignoff, R.J. et. al, Cancer Chemotherapy Pocket Guide, 1998) related to the duration of dosing above a threshold concentration (50nM) (Kearns, C.M. et. al., Seminars in Oncology, 3(6) p.16-23, 1995).

Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate; is commercially available as an injectable solution as TAXOTERE®. Docetaxel is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of paclitaxel *q.v.*, prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree. The dose limiting toxicity of docetaxel is neutropenia.

Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle plant. Vinca alkaloids act at the M phase (mitosis) of the cell cycle by binding specifically to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into microtubules. Mitosis is believed to be arrested in metaphase with cell death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.

Vinblastine, vincaleukoblastine sulfate, is commercially available as VELBAN® as an injectable solution. Although, it has possible indication as a second line therapy of various solid tumors, it is primarily indicated in the treatment of testicular cancer and various lymphomas including Hodgkin's Disease; and lymphocytic and histiocytic lymphomas. Myelosuppression is the dose limiting side effect of vinblastine.

Vincristine, vincaleukoblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN® as an injectable solution. Vincristine is indicated for the treatment of acute leukemias and has also found use in treatment regimens for Hodgkin's and non-Hodgkin's malignant lymphomas. Alopecia and neurologic effects are the

most common side effect of vincristine and to a lesser extent myelosupression and gastrointestinal mucositis effects occur.

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)], commercially available as an injectable solution of vinorelbine tartrate (NAVELBINE®), is a semisynthetic vinca alkaloid. Vinorelbine is indicated as a single agent or in combination with other chemotherapeutic agents, such as cisplatin, in the treatment of various solid tumors, particularly non-small cell lung, advanced breast, and hormone refractory prostate cancers. Myelosuppression is the most common dose limiting side effect of vinorelbine.

Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, cisplatin and carboplatin.

Cisplatin, cis-diamminedichloroplatinum, is commercially available as PLATINOL® as an injectable solution. Cisplatin is primarily indicated in the treatment of metastatic testicular and ovarian cancer and advanced bladder cancer. The primary dose limiting side effects of cisplatin are nephrotoxicity, which may be controlled by hydration and diuresis, and ototoxicity.

Carboplatin, platinum, diammine [1,1-cyclobutane-dicarboxylate(2-)-O,O'], is commercially available as PARAPLATIN® as an injectable solution. Carboplatin is primarily indicated in the first and second line treatment of advanced ovarian carcinoma. Bone marrow suppression is the dose limiting toxicity of carboplatin.

Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan, and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

Cyclophosphamide, 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN®. Cyclophosphamide is indicated as a single agent or in combination with other chemotherapeutic agents, in the treatment of malignant lymphomas, multiple myeloma, and leukemias. Alopecia, nausea,

vomiting and leukopenia are the most common dose limiting side effects of cyclophosphamide.

Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN®. Melphalan is indicated for the palliative treatment of multiple myeloma and non-resectable epithelial carcinoma of the ovary. Bone marrow suppression is the most common dose limiting side effect of melphalan.

Chlorambucil, 4-[bis(2-chloroethyl)amino]benzenebutanoic acid, is commercially available as LEUKERAN® tablets. Chlorambucil is indicated for the palliative treatment of chronic lymphatic leukemia, and malignant lymphomas such as lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease. Bone marrow suppression is the most common dose limiting side effect of chlorambucil.

Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN® TABLETS. Busulfan is indicated for the palliative treatment of chronic myelogenous leukemia. Bone marrow suppression is the most common dose limiting side effects of busulfan.

Carmustine, 1,3-[bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BiCNU®. Carmustine is indicated for the palliative treatment as a single agent or in combination with other agents for brain tumors, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas. Delayed myelosuppression is the most common dose limiting side effects of carmustine.

Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Dacarbazine is indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin's Disease. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dacarbazine.

Antibiotic anti-neoplastics are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death. Examples of antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthrocyclins such as daunorubicin and doxorubicin; and bleomycins.

Dactinomycin, also know as Actinomycin D, is commercially available in injectable form as COSMEGEN®. Dactinomycin is indicated for the treatment of

Wilm's tumor and rhabdomyosarcoma. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dactinomycin.

Daunorubicin, (8S-cis-)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as a liposomal injectable form as DAUNOXOME® or as an injectable as CERUBIDINE®. Daunorubicin is indicated for remission induction in the treatment of acute nonlymphocytic leukemia and advanced HIV associated Kaposi's sarcoma. Myelosuppression is the most common dose limiting side effect of daunorubicin.

Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX® or ADRIAMYCIN RDF®. Doxorubicin is primarily indicated for the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and lymphomas. Myelosuppression is the most common dose limiting side effect of doxorubicin.

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*, is commercially available as BLENOXANE®. Bleomycin is indicated as a palliative treatment, as a single agent or in combination with other agents, of squamous cell carcinoma, lymphomas, and testicular carcinomas. Pulmonary and cutaneous toxicities are the most common dose limiting side effects of bleomycin.

Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins.

Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G_2 phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-ethylidene-β-D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly known as VP-16. Etoposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of testicular and non-small cell lung cancers. Myelosuppression is the most common

side effect of etoposide. The incidence of leucopenia tends to be more severe than thrombocytopenia.

Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-thenylidene-β-D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26. Teniposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia in children. Myelosuppression is the most common dose limiting side effect of teniposide. Teniposide can induce both leucopenia and thrombocytopenia.

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mecaptopurine, thioguanine, and gemcitabine.

5-fluorouracil, 5-fluoro-2,4- (1H,3H) pyrimidinedione, is commercially available as fluorouracil. Administration of 5-fluorouracil leads to inhibition of thymidylate synthesis and is also incorporated into both RNA and DNA. The result typically is cell death. 5-fluorouracil is indicated as a single agent or in combination with other chemotherapy agents in the treatment of carcinomas of the breast, colon, rectum, stomach and pancreas. Myelosuppression and mucositis are dose limiting side effects of 5-fluorouracil. Other fluoropyrimidine analogs include 5-fluoro deoxyuridine (floxuridine) and 5-fluorodeoxyuridine monophosphate.

Cytarabine, 4-amino-1-β-D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. It is believed that cytarabine exhibits cell phase specificity at S-phase by inhibiting DNA chain elongation by terminal incorporation of cytarabine into the growing DNA chain. Cytarabine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other cytidine analogs include 5-azacytidine and 2',2'-difluorodeoxycytidine (gemcitabine). Cytarabine induces leucopenia, thrombocytopenia, and mucositis.

Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available as PURINETHOL®. Mercaptopurine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Mercaptopurine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression

and gastrointestinal mucositis are expected side effects of mercaptopurine at high doses. A useful mercaptopurine analog is azathioprine.

Thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, is commercially available as TABLOID®. Thioguanine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Thioguanine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of thioguanine administration. However, gastrointestinal side effects occur and can be dose limiting. Other purine analogs include pentostatin, erythrohydroxynonyladenine, fludarabine phosphate, and cladribine.

Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β-isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at S-phase and by blocking progression of cells through the G1/S boundary. Gemcitabine is indicated in combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of gemcitabine administration.

Methotrexate, N-[4[[(2,4-diamino-6-pteridinyl) methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair and/or replication through the inhibition of dyhydrofolic acid reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder. Myelosuppression (leucopenia, thrombocytopenia, and anemia) and mucositis are expected side effect of methotrexate administration.

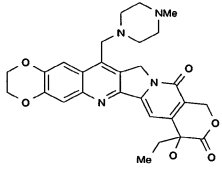
Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin described below.

Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®.

Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I – DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I : DNA : irintecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of the colon or rectum. The dose limiting side effects of irinotecan HCl are myelosuppression, including neutropenia, and GI effects, including diarrhea.

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of singles strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer. The dose limiting side effect of topotecan HCl is myelosuppression, primarily neutropenia.

Also of interest, is the camptothecin derivative of formula A following, currently under development, including the racemic mixture (R,S) form as well as the R and S enantiomers:



A

known by the chemical name "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R,S)-camptothecin (racemic mixture) or "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R)-camptothecin (R enantiomer) or "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin (S enantiomer). Such compounds as well as related compounds are described, including methods of making, in U.S. Patent Nos. 6,063,923; 5,342,947; 5,559,235;

5,491,237 and pending U.S. patent Application No. 08/977,217 filed November 24, 1997.

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children ; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrazole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestrins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5α-reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagagonists such as goserelin acetate and luprolide.

Signal transduction pathway inhibitors are those inhibitors, which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation. Signal tranduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3domain blockers, serine/threonine kinases, phosphotidyl inositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell

growth and are generally termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor –I (IGFI) receptor, macrophage colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene. Several inhibitors of growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides. Growth factor receptors and agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., Exp. Opin. Ther. Patents (2000) 10(6):803-818; Shawver et al DDT Vol 2, No. 2 February 1997; and Lofts, F. J. et al, "Growth factor receptors as targets", New Molecular Targets for Cancer Chemotherapy, ed. Workman, Paul and Kerr, David, CRC press 1994, London.

Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases useful in the present invention, which are targets or potential targets of anti-cancer drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) Journal of Hematotherapy and Stem Cell Research 8 (5): 465 – 80; and Bolen, J.B., Brugge, J.S., (1997) Annual review of Immunology. 15: 371-404.

SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), Journal of Pharmacological and Toxicological Methods. 34(3) 125-32.

Inhibitors of Serine/Threonine Kinases including MAP kinase cascade blockers which include blockers of Raf kinases (rafk), Mitogen or Extracellular Regulated Kinase (MEKs), and Extracellular Regulated Kinases (ERKs); and Protein kinase C family member blockers including blockers of PKCs (alpha, beta,

gamma, epsilon, mu, lambda, iota, zeta). IkB kinase family (IKKa, IKKb), PKB family kinases, akt kinase family members, and TGF beta receptor kinases. Such Serine/Threonine kinases and inhibitors thereof are described in Yamamoto, T., Taya, S., Kaibuchi, K., (1999), Journal of Biochemistry. 126 (5) 799-803; Brodt, P, Samani, A., and Navab, R. (2000), Biochemical Pharmacology, 60. 1101-1107; Massague, J., Weis-Garcia, F. (1996) Cancer Surveys. 27:41-64; Philip, P.A., and Harris, A.L. (1995), Cancer Treatment and Research. 78: 3-27, Lackey, K. et al Bioorganic and Medicinal Chemistry Letters, (10), 2000, 223-226; U.S. Patent No. 6,268,391; and Martinez-Iacaci, L., et al, Int. J. Cancer (2000), 88(1), 44-52.

Inhibitors of Phosphotidyl inositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku are also useful in the present invention. Such kinases are discussed in Abraham, R.T. (1996), Current Opinion in Immunology. 8 (3) 412-8; Canman, C.E., Lim, D.S. (1998), Oncogene 17 (25) 3301-3308; Jackson, S.P. (1997), International Journal of Biochemistry and Cell Biology. 29 (7):935-8; and Zhong, H. et al, Cancer res, (2000) 60(6), 1541-1545.

Also useful in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myoinositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A., (1994) New Molecular Targets for Cancer Chemotherapy ed., Paul Workman and David Kerr, CRC press 1994, London.

Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras activation in cells containing wild type mutant ras , thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), Journal of Biomedical Science. 7(4) 292-8; Ashby, M.N. (1998), Current Opinion in Lipidology. 9 (2) 99 – 102; and BioChim. Biophys. Acta, (19899) 1423(3):19-30.

As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (see Green, M.C. et al, Monoclonal Antibody Therapy for Solid Tumors, Cancer Treat. Rev., (2000), 26(4), 269-286); Herceptin ® erbB2 antibody (see Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kniases, Breast cancer Res., 2000, 2(3), 176-183); and 2CB

VEGFR2 specific antibody (see Brekken, R.A. et al, Selective Inhibition of VEGFR2 Activity by a monoclonal Anti-VEGF antibody blocks tumor growth in mice, Cancer Res. (2000) 60, 5117-5124).

Non-receptor kinase angiogenesis inhibitors may also find use in the present invention. Inhibitors of angiogenesis related VEGFR and TIE2 are discussed above in regard to signal transduction inhibitors (both receptors are receptor tyrosine kinases). Angiogenesis in general is linked to erbB2/EGFR signaling since inhibitors of erbB2 and EGFR have been shown to inhibit angiogenesis, primarily VEGF expression. Thus, the combination of an erbB2/EGFR inhibitor with an inhibitor of angiogenesis makes sense. Accordingly, non-receptor tyrosine kinase inhibitors may be used in combination with the EGFR/erbB2 inhibitors of the present invention. For example, anti-VEGF antibodies, which do not recognize VEGFR (the receptor tyrosine kinase), but bind to the ligand; small molecule inhibitors of integrin ($alpha_v$ $beta_3$) that will inhibit angiogenesis; endostatin and angiostatin (non-RTK) may also prove useful in combination with the disclosed erb family inhibitors. (See Bruns CJ et al (2000), Cancer Res., 60: 2926-2935; Schreiber AB, Winkler ME, and Derynck R. (1986), Science, 232: 1250-1253; Yen L et al. (2000), Oncogene 19: 3460-3469).

Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of formula (I). There are a number of immunologic strategies to generate an immune response against erbB2 or EGFR. These strategies are generally in the realm of tumor vaccinations. The efficacy of immunologic approaches may be greatly enhanced through combined inhibition of erbB2/EGFR signaling pathways using a small molecule inhibitor. Discussion of the immunologic/tumor vaccine approach against erbB2/EGFR are found in Reilly RT et al. (2000), Cancer Res. 60: 3569-3576; and Chen Y, Hu D, Eling DJ, Robbins J, and Kipps TJ. (1998), Cancer Res. 58: 1965-1971.

Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention. Members of the Bcl-2 family of proteins block apoptosis. Upregulation of bcl-2 has therefore been linked to chemoresistance. Studies have shown that the epidermal growth factor (EGF) stimulates anti-apoptotic members of the bcl-2 family (i.e., mcl-1). Therefore, strategies designed to downregulate the expression of bcl-2 in tumors have demonstrated clinical benefit and are now in Phase II/III trials, namely Genta's G3139 bcl-2 antisense oligonucleotide. Such proapoptotic strategies using the antisense oligonucleotide strategy for bcl-2 are discussed in Water JS et al.

(2000), J. Clin. Oncol. 18: 1812-1823; and Kitada S et al. (1994), Antisense Res. Dev. 4: 71-79.

Cell cycle signalling inhibitors inhibit molecules involved in the control of the cell cycle. A family of protein kinases called cyclin dependent kinases (CDKs) and their interaction with a family of proteins termed cyclins controls progression through the eukaryotic cell cycle. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Several inhibitors of cell cycle signalling are under development. For instance, examples of cyclin dependent kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania et al, Exp. Opin. Ther. Patents (2000) 10(2):215-230.

In one embodiment, the cancer treatment method of the claimed invention includes the co-administration a compound of formula I and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof and at least one anti-neoplastic agent, such as one selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, and cell cycle signaling inhibitors.

Because the pharmaceutically active compounds of the present invention are active as AKT inhibitors they exhibit therapeutic utility in treating cancer and arthritis.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from ovarian, pancreatic and prostate.

Isolation and Purification of His-tagged AKT1 (aa 136-480)

Insect cells expressing His-tagged AKT1 (aa 136-480) were lysed in 25 mM HEPES, 100 mM NaCl, 20 mM imidazole; pH 7.5 using a polytron (5 mLs lysis buffer/g cells). Cell debris was removed by centrifuging at 28,000 x *g* for 30 minutes. The supernatant was filtered through a 4.5-micron filter then loaded onto a nickel-chelating column pre-equilibrated with lysis buffer. The column was washed with 5 column volumes (CV) of lysis buffer then with 5 CV of 20% buffer B, where buffer B is 25 mM HEPES, 100 mM NaCl, 300 mM imidazole; pH 7.5. His-tagged AKT1 (aa 136-480) was eluted with a 20-100% linear gradient of buffer B over 10 CV. His-tagged AKT1 (136-480) eluting fractions were pooled and diluted 3-fold with buffer C, where buffer C is 25 mM HEPES, pH 7.5. The sample was then chromatographed over a Q-Sepharose HP column pre-equilibrated with buffer C. The column was washed with 5 CV of buffer C then step eluted with 5 CV 10%D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100% D; where buffer D is 25 mM HEPES, 1000 mM NaCl; pH 7.5. His-tagged AKT1 (aa 136-480) containing fractions were pooled and concentrated in a 10-kDa molecular weight cutoff concentrator. His-tagged AKT1 (aa 136-480) was chromatographed over a Superdex 75 gel filtration column pre-equilibrated with 25 mM HEPES, 200 mM NaCl, 1 mM DTT; pH 7.5. His-tagged AKT1 (aa 136-480) fractions were examined using SDS-PAGE and mass spec. The protein was pooled, concentrated and frozen at –80C.

His-tagged AKT2 (aa 138-481) and His-tagged AKT3 (aa 135-479) were isolated and purified in a similar fashion.

AKT Enzyme Assay

Compounds of the present invention were tested for AKT 1, 2, and 3 protein serine kinase inhibitory activity in substrate phosphorylation assays. This assay examines the ability of small molecule organic compounds to inhibit the serine phosphorylation of a peptide substrate. The substrate phosphorylation assays use the catalytic domains of AKT 1, 2, or 3. AKT 1, 2 and 3 are also commercially available from Upstate USA, Inc. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine residue of a biotinylated synthetic peptide SEQ. ID NO: 1 (Biotin-ahx-ARKRERAYSFGHHA-amide). Substrate phosphorylation was detected by the following procedure:

Assays were performed in 384well U-bottom white plates. 10 nM activated AKT enzyme was incubated for 40 minutes at room temperature in an assay

volume of 20ul containing 50mM MOPS, pH 7.5, 20mM $MgCl_2$, 4uM ATP, 8uM peptide, 0.04 uCi [g-^{33}P] ATP/well, 1 mM CHAPS, 2 mM DTT, and 1ul of test compound in 100% DMSO. The reaction was stopped by the addition of 50 ul SPA bead mix (Dulbecco's PBS without Mg^{2+} and Ca^{2+}, 0.1% Triton X-100, 5mM EDTA, 50uM ATP, 2.5mg/ml Streptavidin-coated SPA beads.) The plate was sealed, the beads were allowed to settle overnight, and then the plate was counted in a Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT).

The data for dose responses were plotted as % Control calculated with the data reduction formula 100*(U1-C2)/(C1-C2) versus concentration of compound where U is the unknown value, C1 is the average control value obtained for DMSO, and C2 is the average control value obtained for 0.1M EDTA. Data are fitted to the curve described by: $y = ((Vmax * x) / (K + x))$ where Vmax is the upper asymptote and K is the IC50.

The pharmaceutically active compounds within the scope of this invention are useful as AKT inhibitors in mammals, particularly humans, in need thereof.

The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring AKT inhibition, which comprises administering an effective compound of Formula (I) or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof. The compounds of Formula (I) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as Akt inhibitors. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid;. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but,

preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of an Akt inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular Akt inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing Akt inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective Akt inhibiting amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use as an Akt inhibitor.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating cancer.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating arthritis.

The invention also provides for a pharmaceutical composition for use as an Akt inhibitor which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in treating arthritis which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer or arthritis, or compounds known to have utility when used in combination with an Akt inhibitor.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

Experimental Details

The compounds of Examples 1 to 104 are readily made according to Schemes 1 to 13 or by analogous methods.

Example 1

Preparation of (S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine

a) ((S)-1-Hydroxymethyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester

Saturated $NaHCO_3$ aqueous solution (3 mL) was added to a solution of (-)-phenylalaninol (1.007 g, 6.66 mmol) and di-*t*-butyl dicarbonate (2.18 g, 9.99 mmol)

in CH_2Cl_2 and the resulting mixture was stirred at room temperature for 3 h. The reaction was complete indicated by TLC. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 times). The combined the organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (hexane/EtOAc 3:1) to give a white solid (1.64 g , 98%).

b) 3-Bromo-2-chloro-5-((S)-2-methyl-3-phenyl-propoxy)-pyridine

DEAD (0.30 mL, 1.87 mmol) was added to a solution of 4-bromo-5-chloro-3-hydroxypyridine (243 mg, 1.17 mmol, Koch, V. Schnatterer, S. *Synthesis*, **1990**, 499-501), compound of Example 1 (a) (440 mg, 1.80 mmol) and Ph_3P (460 mg, 1.80 mmol) in THF (10 mL) at 0 ºC. The resulting mixture was warmed up to room temperature and stirred for 1 h. The reaction was complete indicated by TLC. The reaction mixture was concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 9:1) to give a white solid (450 mg, 87%).

c) 3-Methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester

A mixture of N-Boc-3-methyl-5-bromoindazole (1.11 g, 3.58 mmol), bis(pinacola)diboron (1.0 g, 3.94 mmol), KOAc (527 mg, 5.37mmol), Pd_2dba_3 (49 mg, 0.054 mmol) and PCy_3 (72 mg, 0.26 mmol) in dioxane (21.5 mL) was purged with N_2 and heated at 80 ºC under N_2 for 24 h. The reaction mixture was filtered through celite, which was rinsed with EtOAc. The combined filtrates were concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 9:1) to give a light yellow solid (1.046 g, 74%).

d) 5-[5-((S)-2- *tert* -Butoxycarbonylamino-3-phenyl-propoxy)-2-chloro-pyridin-3-yl]-3-methyl-indazole-1- carboxylic acid *tert*-butyl ester

A mixture of the compound of Example 1(b) (550 mg, 1.24 mmol), compound of Example 1(c) (550 mg, 1.53 mmol), $(Ph_3P)_4Pd$ (143 mg, 0.12 mmol), 2N Na_2CO_3 aqueous solution (0.84 mL) and 1,4-dioxane (10 mL) was degassed and heated at 100 ºC under N_2 overnight. The reaction mixture was filtered through celite, which was rinsed with EtOAc. The combined filtrates were concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 3:1 to 1:1) to give a light yellow solid (585 mg, 80%).

e) {(S)-1-Benzyl-2-[5-(3-methyl-1 *H* -indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethyl}-carbamic acid *tert* -butyl ester

A mixture of the compound of Example 1(d) (196 mg, 0.33 mmol), phenylboronic acid (80.6 mg, 0.66 mmol), $(Ph_3P)_4Pd$ (19 mg, 0.016 mmol), 2N Na_2CO_3 aqueous solution (0.73 mL) and 1,4-dioxane (3 mL) was degassed and irradiated under microwave at 160 ºC for 20 min. The reaction mixture was filtered through celite, which was rinsed with EtOAc. The combined the filtrates were concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 3:1 to 1:1) to give a light yellow solid (101 mg, 57%).

f) (S)-1-Benzyl-2-[5-(3-methyl-1 *H* -indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine

A solution of the compound of Example 1(e) and 0.5 mL of TFA in CH_2Cl_2 (1.5ml) was stirred at room temperature for 30 min, diluted with toluene and concentrated. The residue was taken up into DMSO and purified on reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give a white solid (78mg,78%). ^1H NMR (CD_3OD, 400 MHz) δ 8.49 (d, *J* = 2.8 Hz, 1H), 7.92 (d, *J* = 2.8 Hz, 1H), 7.66 (d, *J* = 0.7 Hz, 1H), 7.40-7.32 (m, 11H), 7.11 (dd, *J* = 8.7, 1.6 Hz), 4.46 (dd, *J* = 10.6, 3.0 Hz, 1H), 4.31 (dd, *J* = 10.6, 5.6 Hz, 1H), 4.03-3.95 (m, 1H), 3.19 (d, *J* = 7.4 Hz, 2H), 2.50 (s, 3H); MS (M+H): 435.2

Example 2

Preparation of (S)-1-Benzyl-2-[6-furan-2-yl-5-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 2-furanboronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.40 (d, *J* = 2.8 Hz, 1H), 7.72 (dd, *J* = 1.4, 0.9 Hz, 1H), 7.61 (d, *J* = 2.8 Hz, 1H), 7.56-7.54 (m, 2H), 7.41-7.31 (m, 7H), 7.28 (dd, *J* = 8.6, 1.6 Hz, 1H), 6.36 (dd, *J* = 3.5, 1.8 Hz, 1H), 5.91 (dd, *J* = 3.5, 0.6 Hz, 1H), 4.48 (dd, *J* = 10.6, 3.0 Hz, 1H), 4.23 (dd, *J* = 10.6, 5.6 Hz, 1H), 4.00-3.90 (m, 1H), 3.16 (d, *J* = 7.6 Hz, 2H), 2.58 (s, 3H); MS (M+H): 425.2

Example 3

Preparation of (S)-1-Benzyl-2-[5,6-bis-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting the compound of Example 1(c) for phenylboronic acid, the title compound was

prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46 (s, 1H), 7.81-7.78 (m, 2H), 7.71 (s, 1H), 7.40-7.27 (m, 13H), 7.19 (dd, J = 8.7, 1.5 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 4.45-4.42 (m, 1H), 4.30-4.25 (m, 1H), 4.01-3.92 (m, 1H), 3.19 (d, J = 6.7Hz, 2H), 2.50 (s, 3H), 2.45 (s, 3H) MS (M+H): 489.2

Example 4

Preparation of (S)-1-Benzyl-2-[6-thiophen-2yl-5- (3-methyl-1H-indazol-5-yl) - pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 2-thiopheneboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47 (d, 1H), 7.90 (s, 1H), 7.68 (d, 1H), 7.48-7.30 (m, 8H), 7.17 (d, 1H), 6.88 (dd, 1H), 4.45 (dd, 1H), 4.32 (dd, 1H), 4.00 (m, 1H), 3.19 (d, 2H), 2.54 (s, 3H). MS (M+H): 441.2

Example 5

Preparation of (S)-1-Benzyl-2-[6-(4-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) - pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 4-chlorophenylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1H), 7.68 (dd, 2H), 7.40-7.29 (m, 6H), 7.22 (m, 4H), 7.06 (m, 1H), 4.40 (dd, 1H), 4.25 (dd, 1H), 3.99-3.95 (m, 1H), 3.19 (d, 2H), 2.53 (s, 3H). MS (M+H): 469.2

Example 6

Preparation of (S)-1-Benzyl-2-[6-(3-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) - pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 3-chlorophenylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.42 (d, 1H), 7.65 (s, 1H), 7.60 (s, 1H), 7.42-7.28 (m, 8H), 7.19 (t, 1H), 7.08 (m, 2H), 4.39 (dd, 1H), 4.26 (dd, 1H), 3.97 (m, 1H), 3.18 (d, 2H), 2.50 (s, 3H). MS (M+H): 469.2

Example 7

Preparation of (S)-1-Benzyl-2-[6-benzyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

a) {(S)-1-Benzyl-2-[6-benzyl-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethyl}-carbamic acid benzyl ester

A mixture of 1(d) (35 mg, 0.059 mmol), BrZnPh (0.59 mL, 0.5 M in THF), and $Pd(Ph_3P)_4$ (6.8 mg, 0.0059 mmol) was purged with N_2, stirred at 75 ºC overnight and cooled to room temperature. Saturated NH_4Cl aqueous solution was added and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 1:1) to give a mixture of 7(a) and {(s)-1-Benzyl-2-[6-chloro-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethyl}-carbamic acid benzyl ester (18mg).

b) (S)-1-Benzyl-2-[6-benzyl-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine

A mixture of 7(a) and {(s)-1-Benzyl-2-[6-chloro-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethyl}-carbamic acid benzyl ester (18 mg), 10% Pd/C (5 mg) and 0.5 mL of MeOH was stirred under a balloon pressure of H_2 overnight. The reaction mixture was filtered through celite, which was rinsed with MeOH. The combined filtrates were concentrated and the residue was purified by reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give 2.3 mg of the title compound. ^1H NMR (CD_3OD, 400 MHz) δ 8.40 (d, 1H), 7.62 (dd, 1H), 7.53 (d, 1H), 7.46 (s, 1H), 7.40-7.27 (m, 6H), 7.18 (m, 3H), 6.88 (m, 2H), 4.35 (dd, 1H), 4.20 (m, 3H), 3.82 (m, 1H), 3.13 (d, 2H), 2.49 (s, 3H), MS (M+H): 449.2

Example 8

Preparation of (S)-1-Benzyl-2-[6-cyclopent-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting cyclopent-1-enylboronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1H), 8.14 (d, 1H), 7.86 (s, 1H), 7.60 (d, 1H), 7.53-7.38(m, 6H), 6.30 (s, 1H), 4.49 (dd, 1H), 4.34 (dd, 1H), 4.00 (m, 1H), 3.17 (d, 2H), 2.60 (s, 3H), 2.52 (m, 2H), 2.24 (m, 2H), 1.90 (m, 2H), MS (M+H): 425.4

Example 9

Preparation of (S)-1-Benzyl-2-[6-cyclopentyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

To the solution of Example 8 (7.8 mg, 0.012 mol) in MeOH (0.5 ml) was added 5 mg of 10% Pd/C. The mixture was stirred under a balloon pressure of H_2 for 1 hr. The reaction mixture was filtered through celite, which was rinsed with MeOH. The combined filtrates were concentrated and the residue was purified by reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give 6 mg (77%) of the title compound. ^1H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1H), 8.05 (d, 1H), 7.80 (s, 1H), 7.65 (dd, 1H)7.55-7.29 (m, 6H), 4.44-4.40 (dd, 1H), 4.30-4.26 (dd, 1H), 3.97 (m, 1H), 3.54-3.45 (m, 1H), 3.15 (d, 2H), 2.61 (s, 3H), 2.10-1.59 (m, 8H), MS (M+H): 427.4

Example 10

Preparation of (S)-1-Benzyl-2-[6-cyclohex-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting cyclohex-1-enylboronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.44 (d, 1H), 8.25 (d, 1H), 7.90 (s, 1H), 7.62 (d, 1H), 7.53 (d, 1H), 7.42-7.30 (m, 5H), 6.27 (t, 1H), 4.49 (m, 1H), 4.35 (m, 1H), 4.00 (m, 1H), 3.17 (d, 2H), 2.61 (s, 3H), 2.26 (m, 2H), 1.83 (m, 2H), 1.61 (m, 2H), 1.53 (m, 2H). MS (M+H): 439.2

Example 11

Preparation of (S)-1-Benzyl-2-[6-cyclohexyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 9, except substituting Example 8 with Example 10, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.41 (d, 1H), 7.83 (d, 1H), 7.74 (s, 1H), 7.63 (d, 1H), 7.40-7.29 (m, 6H), 4.41(dd, 1H), 4.24 (dd, 1H), 3.96 (m, 1H), 3.14 (d, 2H), 2.98 (m, 1H), 1.90-1.62 (m, 7H), 1.48-1.11 (m, 3H). MS (M+H): 441.2

Example 12

Preparation of 3-Methyl-5-[2-phenyl-5-(piperidin-4-ylmethoxy)-pyridin-3-yl]-1H-indazole

a) 6-chloro-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinol

A mixture of 5-bromo-6-chloro-3-pyridinol (1.40 g, 6.70 mmol), 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (2.08 g, 8.04 mmol), $(Ph_3P)_4Pd$ (385 mg, 0.34 mmol), 2N Na_2CO_3 aqueous solution (7.7 mL) and DME (20 mL) was degassed and heated at 80 ºC under N_2 overnight. The reaction mixture was filtered through celite, which was rinsed with EtOAc. The combined filtrates were concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 1:1) to give a light yellow foamy solid (1.23 g, 71%).

b) 5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinol

A mixture of compound of Example 12(a) (1.03 g, 4.75 mmol), phenylboronic acid (695 mg, 5.70 mmol), $(Ph_3P)_4Pd$ (274 mg, 0.24 mmol), 2N Na_2CO_3 aqueous solution (8.5 mL) and 1,4-dioxane (20 mL) was degassed and heated at 100 ºC overnight. The reaction mixture was filtered through celite, which was rinsed with EtOAc. The combined the filtrates were concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 1:1) to give a light yellow solid (846 mg, 70%).

c) 1,1-dimethylethyl 4-({[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}methyl)-1-piperidinecarboxylate

DEAD (0.033 mL, 0.2mmol) was added to a solution of the compound of Example 12(b) (40 mg, 0.13 mmol), 1,1-dimethylethyl 4-(hydroxymethyl)-1-piperidinecarboxylate (42.8mg, 0.2mmol) and Ph_3P (52 mg, 0.2 mmol) in THF (1 mL) at 0 ºC. The resulting mixture was warmed up to room temperature and stirred for 1 h. The reaction was complete indicated by TLC. The reaction mixture was concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 1:1) to give a white solid (45 mg, 69%).

d) 3-methyl-5-{2-phenyl-5-[(4-piperidinylmethyl)oxy]-3-pyridinyl}-1*H*-indazole

A solution of compound of Example 12(c) and 0.5 mL of TFA in CH_2Cl_2 (1.5ml) was stirred at room temperature for 30 min, diluted with toluene and

concentrated. The residue was taken up into DMSO and purified on reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give a white solid (35 mg, 62%). ^1H NMR (CD_3OD, 400 MHz) δ 8.56 (d, 1H), 8.23 (d, 1H), 7.74 (s, 1H), 7.52-7.35 (m, 6H), 7.13 (d, 1H), 4.27 (d, 2H), 3.50 (d, 2H), 3.12 (m, 2H), 2.51 (s, 3H), 2.30 (m, 1H), 2.17 (d, 2H), 1.73 (m, 2H), MS (M+H): 399.4

Example 13

Preparation of 3-[5-(3-Methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-propylamine

Following the procedure of Example 12, except substituting (2-Hydroxy-ethyl)-carbamic acid tert-butyl ester for 1,1-dimethylethyl 4-(hydroxymethyl)-1-piperidinecarboxylate the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.57 (d, 1H), 8.25 (d, 1H), 7.74 (s, 1H), 7.50-7.34 (m, 6H), 7.15 (d, 1H), 4.78 (t, 2H), 3.26 (t, 2H), 2.50 (s, 3H), 2.30 (m, 2H), MS (M+H): 359.2

Example 14

Preparation of (S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-thiophen-2-yl)-pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 5-methylthiophen-2-ylboronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.31(d, 1H), 7.70 (s, 1H), 7.51 (d, 1H), 7.49-7.24 (m, 7H), 6.47 (m, 1H), 6.31 (d, 1H), 4.31 (dd, 1H), 4.17 (dd, 1H), 3.95 (m, 1H), 3.15 (d, 2H), 2.57 (s, 3H), 2.39 (s, 3H). MS (M+H): 455.0

Example 15

Preparation of (S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-furan-2-yl)-pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 5-methylfuran-2-ylboronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.37(s, 1H), 7.70 (m, 2H), 7.62 (m, 1H), 7.49-7.30 (m, 5H), 5.97 (m, 1H), 5.80 (s, 1H), 5.73 (s, 1H), 4.37 (dd, 1H), 4.22 (dd, 1H), 3.96 (m, 1H), 3.17 (d, 2H), 2.55 (s, 3H), 2.26 (s, 3H). MS (M+H): 439.2

Example 16

Preparation of 3-Methyl-5-[2-phenyl-5-(4-pyridin-3-yl-methyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole

a) Trifluoro-methanesulfonic acid 5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yl ester

A solution of compound 12(b) (150 mg, 0.50 mmol) and $PhNTf_2$ (213 mg, 1.2 eq.) in CH_2Cl_2 (5 mL) was added Et_3N (0.14 mL, 2.0 eq.). The resulting mixture was stirred at rt overnight, washed with water, brine, and dried (Na_2SO_4). Removal of the solvent followed by flash column chromatography of the residue on silica gel afforded 198 mg (92%) of the titled compound.

b) 3-Methyl-5-[2-phenyl-5-(4-pyridin-3-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole

A solution of compound Example 16(a) (13.8 mg, 0.032 mmol) and 1-pyridin-3-ylmethyl-piperazine (14 mg, 2.5 eq.) in NMP (0.2 mL) was irradiated with microwave (personal choice synthesizer) at 205 ºC for 30 min. The reaction mixture was loaded on the reversed phase HPLC column and purified (MeCN, H_2O, 0.1% TFA) to give 17.2 mg of white solid (67%). ^1H NMR (CD_3OD, 400 MHz) δ 9.04 (s, 1H), 8.90 (s, 1H), 8.58 (d, 1H), 8.46 (s, 1H), 8.26 (s, 1H), 8.00 (m, 1H), 7.77 (s, 1H), 7.50-7.34 (m, 6H), 7.15 (d, 1H), 4.59 (s, 2H), 3.88 (t, 4H), 3.51 (t, 4H), 2.51 (s, 3H). MS (M+H): 461.4

Example 17

Preparation of 3-Methyl-5-[2-phenyl-5-(4-pyridin-4-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole

Following the procedure of Example 16, except substituting 1-pyridin-4-ylmethyl-piperazine for 1-pyridin-3-ylmethyl-piperazine the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.88(d, 2H), 8.41 (d, 1H), 8.21 (d, 1H), 8.13 (d, 2H), 7.76 (s, 1H), 7.48-7.34 (m, 6H), 7.12 (d, 1H), 4.31 (s, 2H), 3.78 (t, 4H), 3.15 (t, 4H), 2.51 (s, 3H). MS (M+H): 461.4

Example 18

Preparation of [(1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting 3-furanboronic acid for phenylboronic acid, the title compound was prepared. ^1H

NMR (CD_3OD, 400 MHz) δ 8.39 (d, *J* = 2.4 Hz, 1H), 7.72 (s, 1H), 7.57 (s, 1H), 7.53(d, *J* = 8.8 Hz, 1H), 7.41-7.15 (m, 8H), 6.31(dd, *J* = 3.5, 1.8 Hz, 1H), 4.36 (d, *J* = 10.4, 1H), 4.22 (dd, *J* = 10.6, 5.6 Hz, 1H), 4.00-3.94 (m, 1H), 3.16 (m, 2H), 2.57 (s, 3H); MS (M+H): 425.2.

Example 19

Preparation of [(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(5-chloro-2-thienyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting 5-chloro-2-thiopheneboronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.33 (d, 1 H), 7.16 (d, 1 H), 7.49 (d, 1 H), 7.41-7.28 (m, 6 H), 7.26 (d, 1 H), 6.92 (d, 1 H), 6.46 (d, 1 H), 4.32 (dd, 1 H), 4.18 (dd, 1 H), 3.95 (m, 1 H), 3.14 (m, 2 H), 2.58 (s, 3 H), 2.01 (s, 3 H); MS (M+H): 475.2/ 477.2.

Example 20

Preparation of [(1*S*)-2-{[6-(3-aminophenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting (3-aminophenyl)boronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1 H), 7.65 (m, 2 H), 7.42-7.22 (m, 10 H), 7.11 (d, 1 H), 4.39 (m, 1 H), 4.26 (dd, 1 H), 3.98 (m, 1 H), 3.19 (m, 2 H), 2.52 (s, 3 H); MS (M+H): 450.2.

Example 21

Preparation of (S)-1-Benzyl-2-[5-(1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester for compound Example 1(C), the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.53 (d, 1 H), 8.06 (s, 1H), 7.98 (d, 1H), 7.75 (s, 1H), 7.46-7.30 (m, 10

H), 7.13 (d, 1 H), 4.49 (dd, 1 H), 4.33(dd, 1 H), 4.01(m, 1 H), 3.19(d, 2 H); MS (M+H): 421.2.

Example 22

Preparation of (S)-1-Benzyl-2-{6-[3-(3-fluoro-benzyloxy)phenyl]-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy}-ethylamine

a) 2-[3-(3-fluoro-benzyloxy)phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

A mixture of 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (110 mg, 0.50 mmol), 3-fluorobenzyl bromide (0.074 mL, 1.2 eq.), Cs_2CO_3 (179 mg, 1.1 eq) and DMF (3 mL) was stirred at rt for 3 hr, and taken up into EtOAc and water. The organic was separated, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel to give 91 mg (55%) of the titled compound.

b) (S)-1-Benzyl-2-{6-[3-(3-fluoro-benzyloxy)phenyl]-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy}-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting compound of Example 22 (a) for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.46 (s, 1H), 7.80 (s, 1H), 7.65 (s, 1H), 7.40-6.87 (m, 15H), 4.85 (s, 2H), 4.45 (dd, 1H), 4.29 (dd, 1H), 3.99 (m, 1H), 3.18 (d, 2H), 2.52 (s, 3H); MS (M+H): 559.4

Example 23

Preparation of (S)-1-Benzyl-2-[5-(3-phenyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine

a) {(S)-1-Benzyl-2-[5-(1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethyl}-carbamic acid tert-butyl ester

Following the procedure of Example 1(a)-1(e), except substituting 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester for the compound of Example 1(c), the title compound was prepared.

b) {(S)-1-Benzyl-2-[5-(3-iodo-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethyl}-carbamic acid tert-butyl ester

Iodine (53 mg, 1.5 eq.) and KOH (20 mg, 2.5 eq., grounded) were added to a solution of the compound of Example 23(a) (71 mg, 0.14 mmol) in DMF (1.5 mL). The reaction mixture was stirred at rt for 30 min, and taken up into EtOAc and water. The organic layer was separated, washed with brine, dried (Na_2SO_4), and

concentrated. The residue was purified by flash column chromatography on silica gel (2:1 hexane/EtOAc) to give a white solid (37 mg, 42%).

c) (S)-1-Benzyl-2-[5-(3-phenyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(e), except substituting compound of Example 23(b) for compound of Example 1(d), the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.54 (d, 1H), 8.04 (d, 1H), 7.81 (s, 1H), 7.65-7.29 (m, 17H), 4.49 (dd, 1H), 4.36-4.32 (m,1H), 4.03-3.99 (m, 1H), 3.20 (d, 2H); MS (M+H): 497.2.

Example 24

Prepatation of [(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting (1-{[(1,1-dimethylethyl)oxy]carbonyl}-1*H*-pyrrol-2-yl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.35 (d, 1 H), 7.71 (s, 1 H), 7.59 (d, 1 H), 7.52 (d, 2 H), 7.40-7.25 (m, 7 H), 6.82 (d, 2 H), 5.98 (m, 1 H), 5.65 (m, 1 H), 4.35 (dd, 1 H), 4.21 (dd, 1 H), 3.95 (m, 1 H), 3.20 (d, 2 H), 2.67 (s, 3 H); MS (M+H): 424.2.

Example 25

Prepatation of *N*-{3-[5-{[(2S)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}benzamide

a) {(S)-1-Benzyl-2-[5-(3-methyl-1 *H* -indazol-5-yl)-6-(3-nitro-phenyl)-pyridin-3-yloxy]-ethyl}-carbamic acid *tert* -butyl ester

Following the procedure of Example 1(a)-1(e), except substituting 3-nitrophenylboronic acid for phenylboronic acid, the title compound was prepared.

b) {(S)-1-Benzyl-2-[5-(3-methyl-1 *H* -indazol-5-yl)-6-(3-amino-phenyl)-pyridin-3-yloxy]-ethyl}-carbamic acid *tert* -butyl ester

To a solution of the compound of Example 25(a) (260mg, 0.38mmol) in EtOH was added 10% Pd/C (26mg) and the reaction mixture was stirred under a H_2 balloon overnight. The reaction mixture was filtered through celite, which was

rinsed with EtOH. The combined filtrates were concentrated to give the titled product (240mg, 97%).

c) *N*-{3-[5-{[(2S)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}benzamide

A solution of the compound of Example 25(b) (90mg, 0.14mmol), benzoyl chloride (30mg, 0.21mmol) and TEA (0.04ml, 0.28mmol) in 3ml CH_2Cl_2 was stirred at rt for 20min. Solvent was removed and the residue was dissolved in EtOAc, which was washed with $NaHCO_3$, brine and dried. Removal of the solvent followed by flash column chromatography purification of the residue on silica gel afforded the titled compound (78mg, 75%).

d) *N*-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}benzamide

A solution of the compound of Example 25(c) (78mg, 0.10mmol) in 0.6ml TFA and 2ml CH_2Cl_2 was stirred at rt for 20 min, diluted with toluene, and concentrated. The residue was taken up into DMSO and purified on reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give a white solid (40mg, 72%). ^1H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1 H), 7.93 (s, 1 H), 7.86 (m, 2 H), 7.75 (d, 1 H), 7.67 (s, 1 H), 7.62-7.45 (m, 4 H), 7.40-7.30 (m, 6 H), 7.22 (t, 1 H), 7.16 (d, 1 H), 6.98 (d, 1 H), 4.45 (dd, 1 H), 4.29 (dd, 1 H), 4.02 (m, 1 H), 3.18 (d, 2 H), 2.52 (s, 3 H); MS (M+H): 554.4.

Example 26

Prepatation of *N*-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}-2,6-difluorobenzamide

Following the procedure of Example 25, except substituting 2,6-difluorobenzoyl chloride for benzoyl chloride, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.44 (d, 1 H), 7.90 (d, 1 H), 7.72 (d, 2 H), 7.52 (m, 2 H), 7.41-3.33 (m, 6 H), 7.22 (t, 1 H), 7.15-7.11 (m, 3 H), 6.96 (d, 1 H), 4.43 (dd, 1 H), 4.25 (dd, 1 H), 3.99 (m, 1 H), 3.17 (d, 2 H), 2.52 (s, 3 H); MS (M+H): 590.4.

Example 27

Prepatation of *N*-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}cyclohexanecarboxamide

Following the procedure of Example 25, except substituting cyclohexane carbonyl chloride for benzoyl chloride, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.40 (d, 1 H), 7.70 (s, 1 H), 7.65 (s, 2 H), 7.43-7.36 (m, 7 H), 7.14 (t, 1 H), 7.09 (d, 1 H), 6.90 (d, 1 H), 4.12 (d, 1 H), 4.26 (d, 1 H), 3.98 (m, 1 H), 3.17 (d, 2 H), 2.51 (s, 1 H), 2.29 (m,1 H), 1.80 (m, 4 H), 1.47-1.28 (m, 6 H); MS (M+H):560.4.

Example 28

Preparation of [(1*S*)-2-({5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting 2-furanylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47(d, 1 H), 8.03(s, 1 H), 7.80(d, 1 H), 7.66(d, 1 H), 7.45-7.20(m, 11 H), 7.18(dd, 1 H), 6.85(d, 1 H), 6.61(dd, 1 H), 4.43(dd, 1 H), 4.29(dd, 1 H), 3.99-3.07(m, 1 H), 3.18(d, 2 H); MS (M+H): 487.4.

Example 29

Preparation of {(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(2-thienyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine

Following the procedure of Example 23(a)-23(c), except substituting 2-thienylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.45(d, 1 H), 7.88(s, 1 H), 7.75(d, 1 H), 7.48-7.15(m, 14 H), 4.44(dd, 1 H), 4.28(dd, 1 H), 3.97-3.90(m, 1 H), 3.18(d, 2 H); MS (M+H): 503.2.

Example 30

Preparation of [(1*S*)-2-({5-[3-(3-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting 3-furanylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.48(d, 1 H), 7.93(d, 1 H), 7.85(s, 1 H), 7.77(d, 1 H),

7.64(s, 1 H), 7.46(d, 1 H), 7.44-7.25(m, 9 H), 7.22(dd, 1 H), 6.82(d, 1 H), 4.46(dd, 1 H), 4.30(dd, 1 H), 4.28-4.25(m, 1 H), 3.19(d, 2 H); MS (M+H): 487.4.

Example 31

Preparation of [(1*S*)-2-({5-[3-(3-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting 3-thienylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46(d, 1 H), 7.87(d, 1 H), 7.82(s, 1 H), 7.67(d, 1 H), 7.58(s, 1 H), 7.44(d, 1 H), 7.44-7.25(m, 10 H), 7.22(dd, 1 H), 4.45(dd, 1 H), 4.31(dd, 1 H), 4.28-4.25(m, 1 H), 3.18(d, 2 H); MS (M+H): 503.2.

Example 32

Preparation of 3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol

Following the procedure of Example 1(a)-1(f), except substituting 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.42(d, 1 H), 7.81(s, 1 H), 7.68(d, 1 H), 7.42-7.33(m, 6 H), 7.14-7.11(m, 2 H), 6.78-6.72(m, 3 H), 4.44(dd, 1 H0, 4.29(dd, 1 H), 3.99-3.97(m, 1 H), 3.18(d, 2 H), 2.52(s, 3 H); MS (M+H): 451.2.

Example 33

Preparation of [(1*S*)-2-({5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

a) 5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl trifluoroacetate

To a solution of the compound of Example 16(a) (33mg, 0.076mmol) in EtOAc was added Me_3OBF_4 (17mg, 0.115mmol) and stirred for 3h at rt. The reaction was completed indicated by LC/MS. Aqueous $NaHCO_3$ was added. Organic layer was separated and concentrated, and the residue was purified by flash column chromatography (hexane/EtOAc 2:1) to give a white foaming solid (14.7 mg , 43%).

b) 5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinol

To a solution of the compound of the Example 33(a) (14.7mg, 0.033mmol) in 0.5ml MeOH was added 2N NaOH 0.1 mL. The resulting mixture was stirred at rt for 30 min and concentrated. The residue was dissolved in 1 mL of water and neutralized with HOAc. The resulting mixture was extracted by CH_2Cl_2 (5 mL X 3). The organic layers were combined and concentrated, and the residue was purified by flash column chromatography (Hexane/ EtOAc 1:1) to give a white solid (10 mg).

c) 1,1-dimethylethyl [(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]carbamate

DEAD (10.4 uL, 0.066 mmol) was added to a solution of the compound of Example 33(b) (10.8 mg, 0.033 mmol), compound of Example 1 (a) (12.4 mg, 0.049 mmol) and Ph_3P (13.0 mg, 0.049 mmol) in THF (2 mL) at rt. The resulting mixture was stirred at rt overnight. Excess of DEAD and Ph3P were added. The reaction mixture was concentrated and the residue was purified by flash column chromatography (CH_2Cl_2/EtOAc 1:1) to give a white solid (100mg, coeluted with Ph_3P=O).

d) [(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

A solution of the compound of Example 33(c) and 0.2 mL of TFA in CH_2Cl_2 (0.8 ml) was stirred at room temperature for 20 min, diluted with toluene and concentrated. The residue was taken up into DMSO and purified on reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give a white solid (4.5mg, 20% over 3 steps). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.52 (d, 1H), 7.99 (d, 1H), 7.66 (s, 1H), 7.42-7.31 (m, 11H), 7.01 (d, 1H), 4.48 (dd, 1H), 4.33 (dd,1H), 4.12 (s, 3H), 4.02-3.99 (m, 1H), 3.19 (d, 2H), 2.62 (s, 3H); MS (M+H): 449.2

Example 34

Preparation of [(1*S*)-2-({5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting 2-furanylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47(d, 1 H), 8.03(s, 1 H), 7.80(d, 1 H), 7.66(d, 1 H),

7.45-7.20(m, 11 H), 7.18(dd, 1 H), 6.85(d, 1 H), 6.61(dd, 1 H), 4.43(dd, 1 H), 4.29(dd, 1 H), 3.99-3.07(m, 1 H), 3.18(d, 2 H); MS (M+H): 487.4.

Example 35

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1-methyl-1*H*-pyrazol-4-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

a) 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole
To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole(0.19g, 1.0 mmol) in 4 ml DMF was added MeI(0.067 ml, 1.1 eq) and Cs_2CO_3(0.39g, 1.2 eq). The reaction mixture was stirred at RT for 3h. The solution was taken up into EtOAc, washed with water, brine, dried over Na_2SO_4 and concentrated. 150mg crude product was obtained(yield 72%).

b) [(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1-methyl-1*H*-pyrazol-4-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine
Following the procedure of Example 1(a)-1(f), except substituting 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1H), 7.91 (d, 1H), 7.79(d, 1H), 7.55-7.41(m, 2 H), 7.38-7.24(m, 7 H), 4.43 (dd, 1H), 4.28 (dd, 1H), 3.99 (m, 1H), 3.80(s, 3 H), 3.19 (d, 2H), 2.59 (s, 3H). MS (M+H): 439.2.

Example 36

[(1*S*)-2-{[6-(1-[(3-fluorophenyl)methyl]-1*H*-pyrazol-4-yl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

a)1-[(3-fluorophenyl)methyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole
Following the procedure of Example 35(a), except substituting 1-(bromomethyl)-3-fluorobenzene for methyl iodide, the title compound was prepared.

b)[(1*S*)-2-{[6-(1-[(3-fluorophenyl)methyl]-1*H*-pyrazol-4-yl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine
Following the procedure of Example 1(a)-1(f), except substituting 1-[(3-fluorophenyl)methyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47 (d, 1H), 7.92 (d, 1H), 7.73(d, 1H), 7.54(s, 1 H), 7.46(d, 1 H), 7.38-7.20(m, 8 H), 7.02(dd, 1 H), 6.88(d, 1 H), 6.82(d, 1 H), 5.22(s, 2 H), 4.43 (dd, 1H), 4.28 (dd, 1H), 3.99 (m, 1H), 3.18 (d, 2H), 2.54 (s, 3H). MS (M+H): 533.4.

Example 37

((1*S*)-2-phenyl-1-{[(6-phenyl-5-{3-[5-(1-piperazinylmethyl)-2-furanyl]-1*H*-indazol-5-yl}-3-pyridinyl)oxy]methyl}ethyl)amine

a) {5-[(4-{[(1,1-dimethylethyl)oxy]carbonyl}-1-piperazinyl)methyl]-2-furanyl}boronic acid

To a solution of 5-formyl-2-furanyl)boronic acid(0.034g, 0.24 mmol) and 1-Boc-piperazine (0.037 g, 0.20 mmol) in CH_2Cl_2 was added $NaBH(OAc)_3$(0.064 g, 0.30 mmol). The reaction mixture was stirred at rt for a hour. The solution was concentrated and water was then added. The solution was extracted by CH_2Cl_2, dried over Na_2SO_4 and concentrated to give 0.045 g product(72%).

b) ((1*S*)-2-phenyl-1-{[(6-phenyl-5-{3-[5-(1-piperazinylmethyl)-2-furanyl]-1*H*-indazol-5-yl}-3-pyridinyl)oxy]methyl}ethyl)amine

Following the procedure of Example 23(a)-23(c), except the substituting {5-[(4-{[(1,1-dimethylethyl)oxy]carbonyl}-1-piperazinyl)methyl]-2-furanyl}boronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.60 (d, 1H), 8.17 (d, 1H), 8.01(d, 1H), 7.52(d, 1 H), 7.43-7.20(m, 11 H), 6.91(d, 1 H), 6.84(d, 1 H), 4.55(dd, 1 H), 4.43(s, 2 H), 4.28 (dd, 1H), 4.02 (m, 1H), 3.53(br, 4 H), 3.42(br, 4 H), 3.20 (d, 2 H), MS (M+H): 585.4.

Example 38

[(1*S*)-2-({6-(3-furanyl)-5-[3-(2-furanyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

a) 1,1-dimethylethyl [(1*S*)-2-{[6-chloro-5-(1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]carbamate

Following the procedure of Example 1(a)-1(d), except substituting 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester for the compound of Example 1(c), the title compound was prepared.

b) 1,1-dimethylethyl [(1*S*)-2-{[6-chloro-5-(3-iodo-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]carbamate

Following the procedure of Example 23(a)-23(b), except the substituting compound of Example 38(a) for the compound of Example 23(a), the title compound was prepared.

c) 1,1-dimethylethyl [(1*R*)-2-({6-chloro-5-[3-(2-furanyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]carbamate

Following the procedure of Example 23(b)-23(c), except the substituting 2-furanylboronic acid for phenylboronic acid and substituting the compound in Example 38(b) for the compound in Example 23(b), the title compound was prepared.

d)1,1-dimethylethyl acetate - [(1*R*)-2-({6-(3-furanyl)-5-[3-(2-furanyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(d)-1(f), except the substituting the compound 38(c) for the compound 1(d) and substituting 3-furanylboronic acid for phenylboronic acid, the title compound was prepared.

e)[(1*S*)-2-({6-(3-furanyl)-5-[3-(2-furanyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

The compound in Example 38(d)(0.100 g) was dissolved in 5 ml CH_2Cl_2, TFA(1 ml) was added. The mixture was stirred at room temperature for 2 h. Solvent was removed and the residue was purified by reverse HPLC to give 0.042 g product. ^1H NMR (CD_3OD, 400 MHz) δ 8.42(d, 1 H), 8.10(d, 1 H), 7.65(d, 1 H), 7.60(d, 1 H), 7.48(d, 1 H), 7.44-7.32(m, 7 H), 7.20(d, 1 H), 6.96(d, 1 H), 6.63(d, 1 H), 6.31(d, 1 H), 4.37(dd, 1, H), 4.21(dd, 1 H), 3.96(m, 1 H), 3.16(d, 2 H). MS (M+H): 477.2.

Example 39

[(1*S*)-2-({5-(3-methyl-1*H*-indazol-5-yl)-6-[3-(phenyloxy)phenyl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

a) 3-(phenyloxy)phenyl trifluoroacetate

Et_3N (0.48 ml, 1.1 eq.) was added to a solution of m-phenoxyphenol (0.5 mL, 3.11 mmol) and $PhNTf_2$ (1.22g, 1.1 eq.) in DCM (5 mL). The resulting mixture was stirred at rt for 3 hr, washed with water, brine, and dried (Na_2SO_4). Removal of the solvent followed by flash column chromatographic purification of

the residue on silica gel (hexane/EtOAc 95:5) afforded the product as a light yellow clear oil (0.98g, 99%).

b) 4,4,5,5-tetramethyl-2-[3-(phenyloxy)phenyl]-1,3,2-dioxaborolane
Following the procedure of Example 1(c), except the substituting substituting 3-(phenyloxy)phenyl trifluoroacetate for N-Boc-3-methyl-5-bromoindazole, the title compound was prepared.

c) [(1*S*)-2-({5-(3-methyl-1*H*-indazol-5-yl)-6-[3-(phenyloxy)phenyl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine
Following the procedure of Example 1(d)-1(f), except the substituting substituting 4,4,5,5-tetramethyl-2-[3-(phenyloxy)phenyl]-1,3,2-dioxaborolane for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47(d, 1 H), 7.87(d, 1 H), 7.60(d, 1 H), 7.44-7.28(m, 8 H), 7.11-7.08(m, 2 H), 6.98-6.95(m, 3 H), 6.60(d, 1 H), 6.52-6.47(m, 2 H), 4.44(dd, 1 H), 4.25(dd, 1 H), 3.96(m, 1 H), 3.17(d, 2 H), 2.51(s, 3 H). MS (M+H): 527.4.

Example 40

3-[({5-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-2-phenyl-3-pyridinyl)-1*H*-indazol-3-yl]-2-furanyl}methyl)amino]propanenitrile

a) (5-{[(2-cyanoethyl)amino]methyl}-2-furanyl)boronic acid
Following the procedure of Example 37(a), except the substituting 3-aminopropionitrile for 1-Boc-piperazine, the title compound was prepared.

b) 3-[({5-[5-({[(2*S*)-2-amino-3-phenylpropyl]oxy}-2-phenyl-3-pyridinyl)-1*H*-indazol-3-yl]-2-furanyl}methyl)amino]propanenitrile
Following the procedure of Example 23(a)-23(c), except the substituting (5-{[(2-cyanoethyl)amino]methyl}-2-furanyl)boronic acid for phenylboronic acid, the title compound was prepared.^{1}H NMR (CD_3OD, 400 MHz) δ 8.54(d, 1 H), 8.00(dd, 2 H), 7.52(d, 1 H), 7.40-7.35(m, 10 H), 7.24(d, 1 H), 6.89(dd, 2 H), 4.51-4.47(m, 3 H), 4.34(dd, 1 H), 4.02(m, 1 H), 3.47(t, 2 H), 3.35(d, 2 H), 3.00(t, 2 H). MS (M+H): 569.4.

Example 41

[(1*S*)-2-({6-(2-furanyl)-5-[3-(2-furanyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 38(a)-38(d) except substituting 2-furanylboronic acid for 3-furanylboronic acid. the title compound was prepared. ^{1}H

NMR (CD_3OD, 400 MHz) δ 8.54(d, 1 H), 8.12(d, 1 H), 7.64(d, 1 H), 7.60-7.55(m, 2 H), 7.41(d, 1 H), 7.40-7.30(m, 6 H), 6.97(d, 1 H), 6.63(d, 1 H), 6.37(d, 1 H), 5.99(d, 1 H), 4.40(dd, 1 H), 4.36(dd, 1 H), 3.99(m, 1 H), 3.16(d, 2 H). MS (M+H): 477.0.

Example 42

{5-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]-2-thienyl}methanol

a) [5-(hydroxymethyl)-2-thienyl]boronic acid

To a solution of (5-formyl-2-thienyl)boronic acid(31 mg,0.20 mmol) in MeOH(1 ml) was added $NaBH_4$(7.8 mg, 0.20mmol).). The resulting mixture was stirred at rt for 1 hr and filtered through celite. The solution was concentrated and the residue was purified by FCC to give 10 mg product.

b){5-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]-2-thienyl}methanol

Following the procedure of Example 1(a)-1(f), except substituting [5-(hydroxymethyl)-2-thienyl]boronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.37(d, 1 H), 7.73(d, 1 H), 7.49-7.25(m, 8 H), 6.70(d, 1 H), 6.50(d, 1 H), 4.64(d, 2 H), 4.34(dd, 1 H), 4.19(dd, 1 H), 3.95(m, 1 H), 3.19(d, 2 H), 2.57(s, 3 H). MS (M+H): 471.2.

Example 43

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(phenylmethyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine

BnZnBr (0.6 mL, 3.0 eq., 0.5 M in THF) was added to a suspension of the compound in Example23(b) (75 mg, 0.10 mmol) and $Pd(Ph_3P)_4$ (11.6 mg, 10 mol%) at 0 C. The resulting mixture was heated at 50 C for 48 hr, cooled down to rt, and neutralized with saturated NH_4Cl aqueous solution, which was extracted with DCM. The combined organic layers were dried (Na_2SO_4), concentrated and the residue was purified by FCC to give the mono-boc prod as a white foamy solid (14 mg, 23%) and the amine (23 mg, 45%). ^1H NMR (CD_3OD, 400 MHz) δ 8.46(d, 1 H), 7.74(d, 1 H), 7.43-7.15(m, 18 H), 4.40(dd, 1 H), 4.27(dd, 1 H), 4.24(s, 2 H), 3.98(m, 1 H), 3.17(d, 2 H). MS (M+H): 511.4.

Example 44

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1-methyl-1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

A mixture of the compound in Example 1(d) (60 mg, 0.1 mmol), the stannane reagent (41 mg, 1.1 eq.), CsF (33 mg, 2.2 eq.), $Pd(tBu_3P)_2$ (2.6 mg, 5 mol%) and 1,4-dioxane was degassed, sealed and heated at 100 C overnight. The resulting mixture was filtered through celite, which was rinsed with EtOAc. The combined organic layers were dried (Na_2SO_4), concentrated and the residue was purified by FCC to give the product as a light brown oil (40 mg, 63%). ^1H NMR (CD_3OD, 400 MHz) δ 8.53(d, 1 H), 8.32(d, 1 H), 7.61(d, 1 H), 7.48(d, 1 H), 7.40-7.28(m, 6 H), 6.80(dd, 1 H), 6.55(dd, 1 H), 6.30(dd, 1 H), 4.56(dd, 1 H), 4.40(dd, 1 H), 4.06(m, 1 H), 3.20(d, 2 H), 2.95(s, 3 H), 2.50(s, 3 H). MS (M+H): 438.2.

Example 45

5-(5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-2-phenyl-3-pyridinyl)-1*H*-indazol-3-amine

a) 1,1-dimethylethyl 5-(5-{[(2*S*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-phenylpropyl]oxy}-2-phenyl-3-pyridinyl)-3-[(diphenylmethylidene)amino]-1*H*-indazole-1-carboxylate

To a solution of 23(b)(76 mg, 0.1mmol), Pd_2dba_3(2%, 1.8mg), Xantphos(6%, 3.5mg) and Cs_2CO_3(45.6mg, 1.4eq) in 0.5 ml dioxane was added 1,1-diphenylmethanimine(0.024ml, 1.4 eq). The reaction mixture was stirred at 100°C for 20 min. The solution was concentrated and purified by FCC to give 24mg product(30%).

b) 1,1-dimethylethyl 3-amino-5-(5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-2-phenyl-3-pyridinyl)-1*H*-indazole-1-carboxylate

To a solution of Example 50(a)(24 mg, 0.030mmol) in 0.3 ml MeOH was added NH_2OHHCl(2.3 mg, 1.1 eq). The resulting mixture was stirred at rt for overnight. Removed solvent and purified by FCC to give 16 mg product(84%).

c) 5-(5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-2-phenyl-3-pyridinyl)-1*H*-indazol-3-amine

Following the procedure of Example 1(e)-1(f), except substituting the compound in Example 50(b) for the compound in Example 1(d), the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.54(d, 1 H), 7.90(dd, 2 H), 7.41-7.30(m, 12 H), 4.44(dd, 1 H), 4.30(dd, 1 H), 4.00(m, 1 H), 3.32(d, 2 H). MS (M+H): 436.2.

Example 46

[(1*S*)-2-({5-[3-(1-methylethenyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

0.6 Ml ZnCl2 solution(0.5 M in THF) was added to the 0.6 ml solution of bromo(1-methylethenyl)magnesium (0.5 M in THF) at 0°C. White precipitate formed in 5 min. The compound in Example 23(b)(0.075mg, 0.1 mmol) and $Pd(Ph_3P)_4$ were added subsequently. The resulting mixture was heated up to 50 °C for 2.5 h. The mixture was taken up in EtOAc, washed with water, brine and dried over Na2SO4. Removal of the solvent followed by flash column chromatographic purification of the residue on silica gel afforded the product as a light brown solid (0.044g, 78%). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46(d, 1 H), 7.84(d, 1 H), 7.78(d, 1 H), 7.46-7.22(m, 12 H), 5.42(d, 1 H), 5.20(d, 1 H), 4.43(dd, 1 H), 4.29(dd, 1 H), 3.99(m, 1 H), 3.19(d, 2 H), 2.24(s, 3 H). MS (M+H): 461.2.

Example 47

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrazol-4-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.44(d, 1 H), 7.81(d, 1 H), 7.77(d, 1 H), 7.53(d, 1 H), 7.41-7.24(m, 8 H), 4.40(dd, 1 H), 4.27(dd, 1 H), 3.96(m, 1 H), 3.16(d, 2 H), 2.62(s, 3 H). MS (M+H): 425.2.

Example 48

(2*S*)-*N*,*N*-dimethyl-1-({5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy)-3-phenyl-2-propanamine

To a solution of the compound in Example 1 (40 mg, 1.0eq), in 2 ml MeOH was added formaldehyde(4.0eq) and $NaCNBH_3$(4.0eq). The reaction mixture was stirred at rt for 2 hours. The solvent was removed and EtOAc was added. The solution was washed with aq. $NaHCO_3$ and brine and dried over Na_2SO_4. Removal of the solvent followed by flash column chromatographic purification of the residue on silica gel afforded 31mg product(70%).

^{1}H NMR (CD_3OD, 400 MHz) δ 8.48(d, 1 H), 7.88(d, 1 H), 7.66(d, 1 H), 7.41-7.30(m, 11 H), 7.08(d, 1 H), 4.53(dd, 1 H), 4.41(dd, 1 H), 4.14(m, 1 H), 3.21(d, 2 H), 3.14(s, 6 H), 2.50(s, 3 H). MS (M+H): 463.0.

Example 49

[(1*S*)-2-{[3-(3-methyl-1*H*-indazol-5-yl)-2,4'-bipyridin-5-yl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting 4-pyridinylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.63-8.61(m, 3 H), 7.91(d, 2 H), 7.72(d, 1 H), 7.61(d, 1 H), 7.46(d, 1 H), 7.35-7.32(m, 5 H), 7.17(d, 1 H), 4.42(dd, 1 H), 4.28(dd, 1 H), 3.98(m, 1 H), 3.17(d, 2 H), 2.55(s, 3 H). MS (M+H): 436.2.

Example 50

[(1*S*)-2-{[3-(3-methyl-1*H*-indazol-5-yl)-2,3'-bipyridin-5-yl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting 3-pyridinylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.63-8.56(m, 3 H), 8.21(d, 1 H), 7.74-7.68(m, 2 H), 7.62(d, 1 H), 7.46-7.32(m, 6 H), 7.15(d, 1 H), 4.41(dd, 1 H), 4.25(dd, 1 H), 4.01(m, 1 H), 3.19(d, 2 H), 2.54(s, 3 H). MS (M+H): 436.2.

Example 51

[(1*S*)-2-{[5-(3-iodo-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

The title compound was prepared by following the procedure of Example 23(a)-23(b). ^{1}H NMR (CD_3OD, 400 MHz) δ8.44(d, 1 H), 7.65(d, 1 H), 7.40-7.27(m, 12 H), 7.15(d, 1 H), 4.40(dd, 1 H), 4.25(dd, 1 H), 3.98(m, 1 H), 3.17(d, 2 H). MS (M+H): 547.2.

Example 52

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-{3-[(trifluoromethyl)oxy]phenyl}-3-pyridinyl)oxy]-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting {3-[(trifluoromethyl)oxy]phenyl}boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.45(d, 1 H), 7.63-7.60(m, 2 H), 7.42-7.34(m, 8 H), 7.19-7.10(m, 3 H), 4.40(dd, 1 H), 4.24(dd, 1 H), 3.97(m, 1 H), 3.19(d, 2 H), 2.50(s, 3 H). MS (M+H): 519.2.

Example 53

[(1*S*)-2-{[6-(3,5-dimethyl-4-isoxazolyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting (3,5-dimethyl-4-isoxazolyl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47(d, 1 H), 7.70(dd, 2 H), 7.44(d, 1 H), 7.39-7.32(m, 5 H), 7.17(d, 1 H), 4.43(dd, 1 H), 4.25(dd, 1 H), 3.98(m, 1 H), 3.20(d, 2 H), 2.55(s, 3 H), 2.00(s, 3 H), 1.92(s, 3 H). MS (M+H): 454.2.

Example 54

4-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol

Following the procedure of Example 1(a)-1(f), except substituting 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.48(d, 1 H), 8.09(d, 1 H), 7.73(d, 1 H), 7.42-7.32(m, 6 H), 7.18-7.11(m, 3 H), 6.75(d, 2 H), 4.48(dd, 1 H), 4.36(dd, 1 H), 4.02(m, 1 H), 3.19(d, 2 H), 2.54(s, 3 H). MS (M+H): 451.4.

Example 55

2-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol

Following the procedure of Example 1(a)-1(f), except substituting 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.56(d, 1 H), 8.24(d, 1 H), 7.68(s, 1 H), 7.43-7.29(m, 7 H), 7.24(d, 1 H), 7.08(d, 1 H), 6.90(d, 1 H), 6.79(dd, 1 H), 4.52(dd, 1 H), 4.50(dd, 1 H), 4.02(m, 1 H), 3.19(d, 2 H), 2.48(s, 3 H). MS (M+H): 451.2.

Example 56

[(1*S*)-2-{[6-[3-(ethyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting [3-(ethyloxy)phenyl]boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.42(d, 1 H), 7.72(d, 1 H), 7.65(d, 1 H), 7.42-7.36(m, 6 H), 7.19(dd, 1 H), 7.17(d, 1 H), 6.87-6.82(m, 3 H), 4.41(dd, 1 H), 4.26(dd, 1 H), 4.00(m, 1 H), 3.83(q, 2 H), 3.16(d, 2 H), 2.52(s, 3 H), 1.22(t, 3 H). MS (M+H): 479.2.

Example 57

[(1*S*)-2-({5-(3-methyl-1*H*-indazol-5-yl)-6-[3-(methyloxy)phenyl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting [3-(methoxy)phenyl]boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46(d, 1 H), 7.82(d, 1 H), 7.68(d, 1 H), 7.41-7.30(m, 6 H), 7.19(dd, 1 H), 7.11(d, 1 H), 6.92-6.85(m, 3 H), 4.45(dd, 1 H), 4.30(dd, 1 H), 4.02(m, 1 H), 3.62(s, 3 H), 3.19(d, 2 H), 2.53(s, 3 H). MS (M+H): 465.4.

Example 58

{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}(phenyl)methanone

a) Phenyl[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanone
Following the procedure of Example 44(a)-44(b), except the substituting substituting (3-hydroxyphenyl)(phenyl)methanone for m-phenoxyphenol, the title compound was prepared.

b) {3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}(phenyl)methanone
Following the procedure of Example 1(a)-1(f), except substituting phenyl[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanone for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.44(d, 1 H), 7.80(d, 2 H), 7.58-7.40(m, 3 H), 7.46-7.24(m, 10 H), 7.12-7.04(m, 3 H), 4.40(dd, 1 H), 7.24(dd, 1 H), 3.92(m, 1 H), 3.18(d, 2 H), 2.54(s, 3 H). MS (M+H): 539.4.

Example 59

[(1*S*)-2-{[6-{3-[(1-methylethyl)oxy]phenyl}-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting [3-(methylethyl)oxy)phenyl]boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.44(d, 1 H), 7.76(m, 1 H), 7.65(d, 1 H), 7.40-7.33(m, 6 H), 7.22(dd, 1 H), 7.14(dd, 1 H), 6.94(d, 1 H), 6.83(d, 1 H), 6.74(s, 1 H), 4.41(dd, 1 H), 4.29-4.23(m, 2 H), 3.98(m, 1 H), 3.19(d, 2 H), 2.51(s, 3 H). 1.04(d, 6 H) MS (M+H): 493.2.

Example 60

[(1*S*)-2-{[5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting (1- {[(1,1-dimethylethyl)oxy]carbonyl}-1*H*-pyrrol-2-yl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.45(d, 1 H), 8.12(d, 1 H), 7.60-7.52(m, 3 H), 7.40-7.28(m, 6 H), 6.96(d, 1 H), 6.81(d, 1 H), 6.62(d, 1 H), 5.97(d, 1 H), 5.61(d, 1 H), 4.37(dd, 1 H), 4.18(dd, 1 H), 4.00(m, 1 H), 3.19(d, 2 H). MS (M+H): 476.2.

Example 61

[(1*S*)-2-{[6-(2-{[(3-fluorophenyl)methyl]oxy}phenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

a)2-(2-{[(3-fluorophenyl)methyl]oxy}phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol(0.14 g, 0.64 mmol) and Cs_2CO_3(0.26 g, 0.80 mmol) were added to a solution of 1-(bromomethyl)-3-fluorobenzene(.010 g, 0.53 mmol) in DMF(5 ml). The reaction mixture was stirred at rt for 1 h. Removed DMF. The residue was diluted with EtOAc, washed with aq $NaHCO_3$ and brine. Purification by flash column chromatography gave 0.12 g product(yield 71%).

b) [(1*S*)-2-{[6-(2-{[(3-fluorophenyl)methyl]oxy}phenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting 2-(2-{[(3-fluorophenyl)methyl]oxy}phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for phenylboronic acid, the title compound was prepared.^{1}H NMR (CD_3OD, 400 MHz) δ 8.52(d, 1 H), 7.99(d, 1 H), 7.45-7.15(m, 10 H), 7.07-6.95(m, 4 H), 6.77-6.70(m, 2 H), 4.76(s, 2 H), 4.45(dd, 1 H), 4.28(dd, 1 h), 3.99(m, 1 H), 3.18(d, 2 H), 2.37(s, 3 H). MS (M+H): 559.2.

Example 62

[(1*S*)-2-{[6-(4-{[(3-fluorophenyl)methyl]oxy}phenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

a) 2-(4-{[(3-fluorophenyl)methyl]oxy}phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Following the procedure of Example 66(a), except substituting 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol for 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol, the title compound was prepared.

b) [(1*S*)-2-{[6-(4-{[(3-fluorophenyl)methyl]oxy}phenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting 2-(4-{[(3-fluorophenyl)methyl]oxy}phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.40(d, 1 H), 7.65(dd, 2 H), 7.44-7.05(m, 13 H), 6.90(d, 2 H), 5.09(s, 2 H), 4.38(dd, 1 H), 4.24(dd, 1 H), 3.96(m, 1 H), 3.18(d, 2 H), 2.52(s, 3 H). MS (M+H): 559.2.

Example 63

[(1*S*)-2-({5-[3-(5-chloro-2-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting (5-chloro-2-thienyl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.45(d, 1 H), 7.83(d, 1 H), 7.75(d, 1 H), 7.49-7.23(m, 13 H), 7.03(d, 1 H), 4.43(dd, 1 H), 4.26(dd, 1 H), 4.00(m, 1 H), 3.23(d, 2 H). MS (M+H): 537.2.

Example 64

[(1*S*)-2-({5-[3-(4-methyl-2-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting (4-methyl-2-thienyl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.43(d, 1 H), 7.81(d, 1 H), 7.69(d, 1 H), 7.47(d, 1 H), 7.44-7.26(m, 11 H), 7.14(s, 1 H), 7.02(s, 1 H), 4.40(dd, 1 H), 4.24(dd, 1 H), 3.97(m, 1 H), 3.20(d, 2 H), 2.33(s, 3 H). MS (M+H): 517.2.

Example 65

[(1*S*)-2-({5-[3-(5-methyl-2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting (5-methyl-2-furanyl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ8.45(d, 1 H), 7.93(d, 1 H), 7.73(d, 1 H), 7.45-7.29(m, 12 H), 6.71(d, 1 H), 6.19(d, 1 H), 4.40(dd, 1 H), 4.25(dd, 1 H), 3.98(m, 1 H), 3.23(d, 2 H), 2.40(s, 3 H). MS (M+H): 501.4.

Example 66

[(1*S*)-2-({5-[3-(5-methyl-2-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting (5-methyl-2-thienyl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.43(d, 1 H), 7.84(s, 1 H), 7.69(d, 1 H), 7.40-7.18(m, 13 H), 6.83(dd, 1 H), 4.41(dd, 1 H), 4.25(dd, 1 H), 3.96(m, 1 H), 3.19(d, 2 H), 2.54(s, 3 H). MS (M+H): 517.2.

Example 67

[(1*S*)-2-{[6-ethenyl-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting triethenylboroxin for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.44(d, 1 H), 7.78(dd, 2 H), 7.63(d, 1 H), 7.42-7.37(m, 6 H), 6.78(dd, 1 H), 6.23(dd, 1 H), 5.61(dd, 1 H), 4.42(dd, 1 H), 4.27(dd, 1 H), 3.96(m, 1 H), 3.15(d, 2 H), 2.61(s, 3 H). MS (M+H): 385.2.

Example 68

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(1*H*-pyrrol-2-yl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine

Following the procedure of Example 23(a)-23(c), except substituting (1-{[(1,1-dimethylethyl)oxy]carbonyl}-1*H*-pyrrol-2-yl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47(d, 1 H), 7.87(dd, 2 H), 7.41-7.29(m, 11 H), 7.15(dd, 1 H), 6.90(d, 1 H), 6.48(d, 1 H), 6.23(d, 1 H), 4.46(dd, 1 H), 4.31(dd, 1 H), 3.99(m, 1 h), 3.19(d, 2 H). MS (M+H): 586.4.

Example 69

[(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}methyl)ethyl]amine

a) 1,1-dimethylethyl [(1*S*)-2-[(5-bromo-6-chloro-3-pyridinyl)oxy]-1-(1*H*-indol-3-ylmethyl)ethyl]carbamate

Following the procedure of Example 1(a)-1(b), except substituting 1,1-dimethylethyl [(1*S*)-2-hydroxy-1-(1*H*-indol-3-ylmethyl)ethyl]carbamate for ((S)-1-Hydroxymethyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester, the title compound was prepared.

b)1,1-dimethylethyl [(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}methyl)ethyl]carbamate

A solution of the compound of Example 69(a)(100 mg, 1.0 eq), 3-Methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester(1c)(105 mg, 1.1 eq), $Pd(PPh_3)_4$(0.05 eq) and 0.5 ml 5% aqueous $NaHCO_3$ in dioxane was heated at 150°C for 10min in microwave. To the reaction mixture was added another 0.2 ml 5% aqueous $NaHCO_3$, 0.05 eq of $Pd(PPh_3)_4$ and phenylboronic acid(135 mg, 1.2 eq). The reaction mixture was heated at 150 °C for 10 min in microwave. The reaction mixture was concentrated and purified by flash column chromatography (30%-50%-60%hexane/EtOAc) to give 86 mg product (yield 72%).

c) [(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}methyl)ethyl]amine

The solution of 69(b) in 5 ml CH_2Cl_2 was added 1 ml TFA . The reaction mixture was stirred at room temperature for 1 h. The solution was concentrated and crude product was purified by reverse phase HPLC. ^1H NMR (CD_3OD, 400 MHz) δ 8.45(d, 1 H), 7.83(d, 1 H), 7.63-7.61(m, 2 H), 7.41-7.27(m, 9 H), 7.16(dd, 1 H), 7.13-7.03(m, 2 H), 4.50(dd, 1 H), 4.38(dd, 1 H), 4.04(m, 1 H), 3.36(d, 2 H), 2.50(s, 3 H). MS (M+H): 474.4.

Example 70

5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-*N*-(3-phenylpropyl)-3-pyridinamine

a)5-bromo-6-chloro-*N*-(3-phenylpropyl)-3-pyridinamine

To the solution of 5-bromo-6-chloro-3-pyridinamine(0.200g, 0.97 mmol) in 5 ml CH_2Cl_2 was added 3-phenylpropanal(0.195 g, 1.45mmol) followed by $Na(OAc)_3BH$(0.411g, 1.94 mmol). The reaction mixture was stirred at room temperature for 1h. The solution was quenched with water (5 ml) and product was extracted with CH_2Cl_2 (5 mlx3). The organic layer was dried over Na_2SO_4, concentrated. The compound was purified by flash column chromatography to give 0.136g product (yield 50%).

b)5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-*N*-(3-phenylpropyl)-3-pyridinamine

Following the procedure of Example 69(a)-69(c), except substituting the compound in Example 70(a) for the compound in Example 69(a), the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ8.54(s, 1 H), 7.56(d, 1 H), 7.38-7.06(m, 12 H), 7.04(d, 1 H), 3.29(t, 2 H), 2.80(t, 2 H), 2.58(s, 3 H), 2.07(m, 2 H). MS (M+H): 419.2.

Example 71

5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-*N*-(3-phenylbutyl)-3-pyridinamine

Following the procedure of Example 70 except substituting 3-phenylbutanal for 3-phenylpropanal, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46(s, 1 H), 7.53(s, 1 H), 7.38-7.16(m, 12 H), 7.02(d, 1 H), 3.15(dt, 2 H), 2.89(m, 1 H), 2.58(s, 3 H), 2.02(m, 2 H), 1.33(d, 3 H). MS (M+H): 433.4.

Example 72

[(2*S*)-2-amino-3-phenylpropyl][5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine

a) 1,1-dimethylethyl [(1*S*)-2-[(5-bromo-6-chloro-3-pyridinyl)amino]-1-(phenylmethyl)ethyl]carbamate

Following the procedure of Example 70(a) except for substituting N-Boc-(2*S*)-2-amino-3-phenylpropanal for 3-phenylpropanal, the title compound was prepared.

b)1,1-dimethylethyl [(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amino}-1-(phenylmethyl)ethyl]carbamate

Following the procedure of Example 70(b) except for substituting the compound in Example 77(a) for the compound in Example 70(a), the title compound was prepared.

c)[(2*S*)-2-amino-3-phenylpropyl][5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine

To a solution of compound in Example 72(b)(0.102 g) in 5 ml CH_2Cl_2 was added 1 ml TFA. The reaction mixture was stirred at room temperature for 1h. The solution was concentrated under vacumm and crude product was purified by reverse phase HPLC. 0.080g product was obtained (yield 46%, 2 steps). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.04(d, 1 H), 7.64(d, 2 H), 7.45-7.08(m, 11 H), 7.06(d, 1 H), 3.06(m, 1 H), 3.60(m, 2 H), 3.11(m, 2 H), 2.51(s, 3 H). MS (M+H): 434.2.

Example 73

[(2*S*)-2-amino-3-phenylpropyl][6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]amine

Following the procedure of Example 72 except for substituting 3-furanboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.98(d, 1 H), 7.73(s, 1 H), 7.55-7.50(m, 4 H), 7.33-7.12(6 h), 6.26(d, 1 H), 3.79(m, 2 H), 3.08(m, 2 H), 2.59(s, 3 H). MS (M+H): 424.2.

Example 74

((1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-{[(phenylmethyl)oxy]methyl}ethyl)amine

Following the procedure of Example 70(a)-70(b), except substituting phenoxy acetaldehyde for 3-phenylpropanal and substituting 3-furanboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.41(d, 1 H), 7.74(d, 1 H), 7.70(d, 1 H), 7.54(d, 1 H), 7.41-7.26(8 H), 6.31(dd, 1 H), 4.65(s, 2 H), 4.47(m, 1 H), 4.40(m, 1 H), 3.90-3.81(m, 3 H), 2.58(s, 3 H). MS (M+H): 455.0.

Example 75

N-[(2*S*)-2-amino-3-phenylpropyl]-*N*-[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]methanesulfonamide

a)1,1-dimethylethyl [(1*S*)-2-[(5-bromo-6-chloro-3-pyridinyl)(phenylsulfonyl)amino]-1-(phenylmethyl)ethyl]carbamate

To a solution of the compound in Example 72(a)(0.150g, 0.34mmol) in 3 ml CH_2Cl_2 was added 0.1 ml Et_3N(0.70mmol) followed by 0.052 ml benzosulfonic acid(0.41 mmol). The reaction mixture was stirred at room temperature for 1 h, and taken up into CH_2Cl_2 and water. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel to give 0.160 g product(yield 81%).

b) *N*-[(2*S*)-2-amino-3-phenylpropyl]-*N*-[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]methanesulfonamide

Following the procedure of Example 72(b)-72(c) except for substituting the compound in Example 80(a) for the compound in Example 77(a), the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.73(d, 1 H), 7.92(d, 1 H), 7.50(s, 1 H), 7.36-7.01(m, 11 H), 6.99(d, 1 H). 4.07(d, 2 H), 3.71(m, 1 H), 3.11-2.95(m, 4 H), 2.92(m, 1 H), 2.51(s, 3 H). MS (M+H): 512.4.

Example 76

5-(3-methyl-1*H*-indazol-5-yl)-*N*-[2-methyl-2-(phenylthio)propyl]-6-phenyl-3-pyridinamine

Following the procedure of Example 70(a)-70(b), except substituting 2-methyl-2-(phenylthio)propanal for 3-phenylpropanal, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.52(d, 1 H), 7.59-7.26(m, 13 H), 7.03(dd, 1 H), 3.10(s, 2 H), 2.55(s, 3 H), 1.38(s, 6 H). MS (M+H): 465.2.

Example 77

[(1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(1*H*-indol-3-ylmethyl)ethyl]amine

Following the procedure of Example 69(a)-69(c), except substituting 3-furanboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.38(d, 1 H), 7.68(d, 1 H), 7.59-7.57(m, 2 H), 7.52(d, 1 H), 7.40-7.35(m, 2 H), 7.25-7.22(m, 3 H), 7.14(dd, 1 H), 7.04(dd, 1 H), 6.30(dd, 1 H), 4.41(dd, 1 H), 4.28(dd, 1 H), 4.00(m, 1 H), 3.37(d, 2 H), 2.57(s, 3 H). MS (M+H): 464.4.

Example 78

((1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-{[(phenylmethyl)oxy]methyl}ethyl)amine

Following the procedure of Example 1(a)-1(f), except substituting 1,1-dimethylethyl ((1*S*)-2-hydroxy-1-{[(phenylmethyl)oxy]methyl}ethyl)carbamate for 1,1-dimethylethyl [(1*R*)-2-hydroxy-1-(phenylmethyl)ethyl]carbamate, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.45(d, 1 H), 7.80(d, 1 H), 7.66(d, 1 H), 7.43-7.29(m, 11 H), 7.12(dd, 1 H), 4.66(s, 2 H), 4.54-4.43(m, 2 H), 3.94-3.93(m, 1 H), 3.90-3.82(m, 2 H), 2.50(s, 3 H). MS (M+H): 465.4.

Example 79

(2*S*)-2-amino-3-{[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-propanol

To a solution of the compound in Example 78 (250mg) in 5 ml EtOH was added Pd/C(200mg). The reaction mixture was charged with vac/H_2/vac/H_2/vac/H_2. The reaction mixture eas heated at 50°C overnight. The mixture was then filtered. The resulted organic solution was concentrated in vacuo. Separation by flash column chromatography provided 188mg product(yield 87%). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.44(d, 1 H), 7.75(d, 1 H), 7.65(s, 1 H), 7.35-7.28(m, 6 H), 7.10(dd, 1 H), 4.52-4.40(m, 2 H), 3.95-3.85(m, 2 H), 3.83(m, 1 H), 2.51(s, 3 H). MS (M+H): 375.4.

Example 80

5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-*N*-[(2*S*)-2-pyrrolidinylmethyl]-3-pyridinamine

Following the procedure of Example 72 except for substituting N-Boc-(2*S*)-2-pyrrolidinylacetaldehyde for N-Boc-(2*S*)-2-amino-3-phenylpropanal, the title compound was prepared.^{1}H NMR (CD_3OD, 400 MHz) δ 8.16(d, 1 H), 7.75(d, 1 H), 7.68(d,1 H), 7.40-7.28(m, 6 H), 7.12(d, 1 H), 3.98(m, 1 H), 3.67(m, 2 H), 3.39(m, 1

H), 3.32(s, 3 H), 2.46(m, 1 H), 2.17(m, 2 H), 1.88(m, 1 H), 1.32(m, 1 H). MS (M+H): 384.2.

Example 81

((2*S*)-2-amino-3-{4-[(phenylmethyl)oxy]phenyl}propyl)[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine

Following the procedure of Example 70(a)-70(b), except substituting Boc-tyr(bzl)-aldehyde for 3-phenylpropanal, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ8.03(d, 1 H), 7.67(d, 1 H), 7.63(d, 1 H), 7.44-7.32(m, 13 H), 7.26(dd, 1 H), 6.93(d, 2 H), 4.89(s, 2 H), 4.00(m, 1 H), 3.60(m, 2 H), 3.02(m, 2 H), 2.51(s, 3 H). MS (M+H): 540.6.

Example 82

[(2*S*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine

a) 1,1-dimethylethyl [(1*S*)-2-[(5-bromo-6-chloro-3-pyridinyl)amino]-1-(phenylmethyl)ethyl]carbamate

Following the procedure of Example 70(a) except for substituting N-Boc-(2*S*)-2-amino-3-phenylpropanal for 3-phenylpropanal, the title compound was prepared.

b)[(2*S*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine

A solution of the compound in Example 82(a)(116mg, 1.0 eq), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester(105 mg, 1.1 eq), $Pd(PPh_3)_4$(0.05 eq) and 0.5 ml 5% aqueous $NaHCO_3$ in dioxane was heated at 150°C for 10min in microwave. To the reaction mixture was added another 0.2 ml 5% aqueous $NaHCO_3$, 0.05 eq of $Pd(PPh_3)_4$ and phenylboronic acid(135 mg, 1.2 eq). The reaction mixture was heated at 150 °C for another10 min in microwave. The solution was concentrated and purified by flash column chromatography give 81 mg product (yield 72%).

c) [(2*S*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine

The solution of 82(b)(81 mg) in 5 ml CH_2Cl_2 was added 1 ml TFA . The reaction mixture was stirred at room temperature for 1 h. The solution was concentrated and crude product was purified by reverse phase HPLC to give 30 mg of the title compound. . ^{1}H NMR (CD_3OD, 400 MHz) δ 8.11(d, 1 H), 8.03(d, 1 H), 7.66(d, 1 H), 7.59(d, 1 H), 7.47-7.29(m, 10H), 7.11(dd, 2 H), 3.84(m, 1 H), 3.54(m, 2 H), 3.13(m, 2 H). MS (M+H): 420.2.

Example 83

[(2*S*)-2-amino-3-phenylpropyl][6-(3-furanyl)-5-(1*H*-indazol-5-yl)-3-pyridinyl]amine

Following the procedure of Example 82 except for substituting 3-furanylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ8.16(d, 1 H), 8.00(d, 1 H), 7.79(d, 1 H), 7.63(dd, 1 H), 7.51(m, 3 H), 7.30-7.20(m, 6 H), 6.25(d, 1 H), 4.00(m, 1 H), 3.57-3.54(m, 2 H), 3.13-3.01(m, 2 H). MS (M+H): 410.2.

Example 84

[(2*S*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-(3-thienyl)-3-pyridinyl]amine

Following the procedure of Example 82 except for substituting 3-thienylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ8.12(d, 1 H), 7.99(d, 1 H), 7.75(d, 1 H), 7.61-7.51(m, 3 H), 7.40-7.15(m, 6 H), 6.79(dd, 1 H), 3.82(m, 1 H), 3.62-3.53(m, 2 H), 3.15-3.02(m, 2 H), MS (M+H):426.2.

Example 85

2-[5-[[(2*S*)-2-amino-3-phenylpropyl]amino}-3-(1*H*-indazol-5-yl)-2-pyridinyl]phenol

Following the procedure of Example 82 except for substituting 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.06(d, 1 H), 7.99(d, 1 H), 7.69(d, 1 H), 7.63(d, 1 H), 7.43(dd, 1 H), 7.37-7.15(m, 6 H), 6.98(dd, 1 H), 6.88(dd, 1 H), 6.74(t, 1 H), 3.82(m, 1 H), 3.63-3.52(m, 2 H), 3.14-3.03(m, 2 H). MS (M+H):436.2.

Example 86

2-[5-[[(2*S*)-2-amino-3-phenylpropyl]amino}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol

Following the procedure of Example 82 except for substituting 3-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester(1c) for 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester and substituting 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.99(d, 1 H), 7.67(d, 1 H), 7.61(d, 1 H), 7.37-7.20(8 H), 6.99(d, 1 H), 6.89(d, 1 H), 3.85(m, 1 H), 3.60-3.57(m, 2 H), 3.11-3.07(m, 2 H), 2.49(s, 3 H). MS (M+H):450.2.

Example 87

[(2*S*)-2-amino-3-phenylpropyl][5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]amine

Following the procedure of Example 82 except for substituting 3-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester(1c) for 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester and substituting 1*H*-pyrrol-2-ylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.88(d, 1 H), 7.69(d, 1 H), 7.55(d, 1 H), 7.47(d, 1 H), 7.30-7.15(m, 6 H), 6.86(dd, 1 H), 6.29(dd, 1 H), 6.20(dd, 1 H), 3.79(m, 1 H), 3.56-3.52(m, 2 H), 3.10-3.05(m, 2 H), 2.57(s, 3 H). MS (M+H):423.0.

Example 88

[(2*S*)-2-amino-3-phenylpropyl][5-(3-methyl-1*H*-indazol-5-yl)-6-(5-methyl-2-thienyl)-3-pyridinyl]amine

Following the procedure of Example 82 except for substituting 3-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester(1c) for 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester and substituting (5-methyl-2-thienyl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.97(d, 1 H), 7.71(d, 1 H), 7.49(d, 1 H), 7.40-7.18(m, 8 H), 7.03(d, 1 H), 6.73(d, 1 H), 3.78(m, 1 H), 3.55-3.37(m, 2 H), 3.09-3.02(m, 2 H), 2.58(s, 3 H), 2.38(s, 3 H). MS (M+H): 454.0.

Example 89

[(2*R*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-(3-thienyl)-3-pyridinyl]amine

Following the procedure of Example 82 except for substituting N-Boc-(2*R*)-2-amino-3-phenylpropanal for N-Boc-(2*S*)-2-amino-3-phenylpropanal and substituting 3-thienylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.12(d, 1 H), 8.00(d, 1 H), 7.75(d, 1 H), 7.61-7.51(m, 3 H), 7.40-7.15(m, 6 H), 6.79(dd, 1 H), 3.80(m, 1 H), 3.62-3.53(m, 2 H), 3.15-3.02(m, 2 H), MS (M+H):426.2.

Example 90

2-[5-[[(2*S*)-2-amino-3-(1*H*-indol-3-yl)propyl]oxy]-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol

Following the procedure of Example 69 except for substituting 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.54(d, 1 H), 8.24(d, 1 H), 7.63(m, 2 H), 7.48-7.05(m, 7 H), 6.90(d, 1 H), 6.78(dd, 1 H), 4.58(dd, 1 H), 4.48(dd, 1 H), 4.05(m, 1 H), 3.32(d, 2 H), 2.48(s, 3 H). MS (M+H):490.2.

Example 91

[(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}methyl)ethyl]amine

Following the procedure of Example 69 except for substituting 1*H*-pyrrol-2-ylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ8.34(d, 1 H), 7.70(dd, 2 H), 7.62(d, 1 H), 7.50(d, 1 H), 7.38(d, 1 H), 7.23(m, 1 H), 7.17(dd, 1 H), 7.04(dd, 1 H), 6.83(dd, 1 H), 6.08(dd, 1 H), 5.81(dd, 1 H), 4.44(dd, 1 H), 4.32(dd, 1 H), 4.02(m, 1 H), 3.30(d, 2 H), 2.57(s, 3 H). MS (M+H):463.2.

Example 92

[(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-(5-methyl-2-thienyl)-3-pyridinyl]oxy}methyl)ethyl]amine

Following the procedure of Example 69 except for substituting (5-methyl-2-thienyl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.38(d, 1 H), 7.68(d, 1 H), 7.60(dd, 2 H), 7.45(m, 2 H), 7.32(d, 1 H), 7.25(m, 2 H), 7.12(dd,1 H), 7.05(dd, 1 H), 6.53(dd, 1 H), 6.49(dd, 1 H), 4.38(dd, 1 H), 4.29(dd, 1 H), 4.00(m, 1 H), 3.28(d, 2 H), 2.60(s, 3 H), 2.39(s, 3 H). MS (M+H): 493.2.

Example 93

[(1*S*)-2-([6-ethyl-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

In a solution of the compound in Example 67(100mg) in 10 ml EtOH was added 20 mg 10% Pd/C. The solution was then charged with H_2 under 1atm(ballon) and stirred at room temperature for 5h. The mixture was then filtered by celite. The resulted organic solution was concentrated in vacuo. Separation by flash column chromatography provided 88 mg product. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.48(d, 1 H), 7.81(m, 1 H), 7.66(s, 1 H), 7.65(d, 1 H), 7.45-7.31(m, 6 H), 4.42(dd, 1 H), 4.28(m, 1 H), 3.97(m, 1 H), 3.15(d, 2 H), 2.97(m, 2 H), 2.61(s, 3 H), 1.20(t, 3 H). MS (M+H):387.4.

Example 94

[(1*S*)-2-{[6-(3-furanyl)-5-(1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f) except for substituting 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester for the compound in Example 1(c) and substituting 3- furanylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ8.38(d, 1 H), 8.12(s, 1 H), 7.76(s, 1 H), 7.60(d, 1 H), 7.45(d, 1 H), 7.34-7.27(m, 7 H), 7.15(s, 1 H), 6.29(dd, 1 H), 4.33(dd, 1 H), 4.18(dd, 1 H), 3.95(m, 1 H), 3.16(dd, 2 H). MS (M+H): 411.2.

Example 95

[(1*S*)-2-{[5-(3-ethenyl-1*H*-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c) except for substituting 3-furanylboronic acid for phenylboronic acid in Example 23(a) and substituting triethenylboroxin for phenylboronic acid in Example 23(b)-23(c), the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.41(d, 1 H), 7.95(s, 1 H), 7.62-7.57(m, 2 H), 7.40-7.26(m, 8 H), 7.06(dd, 1 H), 6.29(d, 1 H), 6.05(dd, 1 H), 5.53(d, 1 H), 4.39(dd, 1), 4.22(dd, 1 H), 3.96(m, 1 H), 3.32(d, 2 H). MS (M+H):437.4.

Example 96

[(1*S*)-2-{[5-(3-ethyl-1*H*-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 93 except for substituting the compound in Example 95 for the compound in Example 67, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.41(d, 1 H), 7.74(s, 1 H), 7.69(d, 1 H), 7.54(d, 1 H), 7.42-7.28(m, 8 H), 6.29(dd, 1 H), 4.38(dd, 1 H), 4.23(dd, 1 H), 3.96(m, 1 H), 3.18(d, 2 H), 3.01(q, 2 H), 1.38(t, 1 H). MS (M+H):439.4.

Example 97

[(1*S*)-2-({6-(3-furanyl)-5-[3-(3-pyridinyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c) except for substituting 3-furanylboronic acid for phenylboronic acid in Example 23(a) and substituting 3-pyridinylboronic acid for phenylboronic acid in Example 23(b)-23(c), the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.29(s, 1 H), 8.84(s, 1 H), 8.73(d, 1 H), 8.40(d, 1 H), 8.09(s, 1 H), 7.93(d, 1 H), 7.72(d, 1 H), 7.53(d, 1 H),

7.42-7.28(m, 7 H), 7.20(d, 1 H), 6.33(dd, 1 H), 4.34(dd, 1 H), 4.19(dd, 1 H), 3.94(m, 1 H), 3.16(d, 2 H). MS (M+H):488.2.

Example 98

[(1*S*)-2-{[6-methyl-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f) except for substituting Methylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.51(d, 1 H), 8.12(d, 1 H), 7.86(d, 1 H), 7.67(d, 1 H), 7.48(d, 1 H), 7.40-7.31(m, 5 H), 4,45(dd, 1 H), 4,32(dd, 1 H), 4.00(m, 1 H), 3.16(d, 2 H), 2.67(s, 3 H), 2.62(s, 3 H). MS (M+H):373.0.

Example 99

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-[2-(methyloxy)phenyl]-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f) except for substituting 2-methoxyphenylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46(d, 1 H), 7.93(d, 1 H), 7.42(d, 1 H), 7.41-7.28(m, 7 H), 7.36(d, 1 H), 7.20(d, 1 H), 7.01(dd, 1 H), 6.92(d, 1 H), 4.45(dd, 1 H), 4.30(dd, 1 H), 4.00(m, 1 H), 3.50(s, 3 H), 3.20(d, 2 H), 2.45(s, 3 H). MS (M+H): 465.2.

Example 100

[(1*S*)-2-{[6-[2-(ethyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f) except for substituting 2-ethyloxyphenylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.49(d, 1 H), 8.01(d, 1 H), 7.57(s, 1 7.42-7.29(m, 8 H), 7.20(d, 1 H), 7.02(dd, 1 H), 6.90(d, 1 H), 4.47(dd, 1 H), 4.33(dd, 1 H), 4.01(m, 1 H), 3.69(q, 2 H), 3.32(d, 2 H), 2.45(s, 3 H), 1.10(t, 3 H). MS (M+H): 479.4.

Example 101

[(1*S*)-2-{[6-[5-chloro-2-(methyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f) except for substituting 5-chloro-2-(methyloxy)phenylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.41(d, 1 H), 7.72(d, 1 H), 7.53(d, 1

H), 7.43-7.33(m, 8 H), 7.19(d, 1 H), 6.82(d, 1 H), 4.43(dd, 1 H), 4.25(dd, 1 H), 3.96(m, 1 H), 3.19(d, 2 H), 2.47(s, 3 H). MS (M+H): 499.4.

Example 102

[(1*S*)-2-{[6-[5-fluoro-2-(propyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f) except for substituting 5-fluoro-2-(propyloxy)phenylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46(d, 1 H), 7.84(d, 1 H), 7.59(d, 1 H), 7.42-7.33(m, 6 H), 7.19(dd, 1 H), 7.09(m, 2 H), 6.87(dd, 1 H), 4.43(dd, 1 H), 4.28(dd, 1 H), 4.00(m, 1 H), 3.53(t, 2 H), 3.18(d, 2 H), 2.48(s, 3 H), 1.51(m, 2 H), 0.78(t, 3 H). MS (M+H): 511.4.

Example 103

[(1*S*)-2-({5-[3-(1-methylethyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 93 except for substituting the compound in Example 46 for the compound in Example 67, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47(d, 1 H), 7.88(d, 1 H), 7.60(s, 1 H), 7.45-7.24(m, 12 H), 4.44(dd, 1 H), 4.28(dd, 1 H), 3.99(m, 1 H), 3.28(m, 1 H), 3.18(d, 2 H), 1.31(d, 6 H). MS (M+H): 463.4.

Example 104

[(1*S*)-2-{[5-(6-fluoro-3-methyl-1*H*-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

a)1-(5-bromo-2,4-difluorophenyl)ethanone

To a solution of 1,5-dibromo-2,4-difluorobenzene(Nucleosides, Nucleotides & nucleic Acid, 201(1&2), 11-40(2001)) (8.8 g, 32.4 mmol) in diethylether(60 ml), 1.6 M n-BuLi in Hexane(24.3 ml, 1.2 eq) was added at –78°C under N_2 atmosphere. After stirring the reaction mixture at –78 °C for 30 min, *N*-methyl-*N*-(methyloxy)acetamide (5.0 g, 1.5 eq) was dropped into to quench the reaction. The reaction mixture was stirred at the same temperature for further 30 min. After added acetic acid((5.2 ml), water (78 ml), the reaction mixture was extracted with diethylether. The obtained organic phase was washed by 0.2 N HCl aqueous, water, saturated $NaHCO_3$ aqueous and saturated NaCl aqueous, and dried with $MgSO_4$. After removing the solvent under reduced pressure, the residue was

purified by Silica gel chromatography (n-Hexane/EtOAc = 49/1). Desired compound was obtained as pale yellow oil (4.94 g, 65%).

b)1-(5-bromo-2,4-difluorophenyl)ethanone hydrazone

H_2NNH_2 (0.80 ml, 25.5 mmol) was added to a solution of 1-(5-bromo-2,4-difluorophenyl)ethanone (4.72 g, 20.3 mmol) in EtOH (50 ml). The resulting reaction mixture was stirred at RT overnight and evaporated to give dride light yellow solid, which was recrystalized in MeOH to give 1.8 g white crystaline. Mother liquid was concentrated and purified by flash column chromatography to give a total of 3.85 g solid (76%)

c) 5-bromo-6-fluoro-3-methyl-1*H*-indazole

A solution of 1-(5-bromo-2,4-difluorophenyl)ethanone hydrazone (2.16 g, 8.7 mmol) in pyridine (87 ml) was heated up in sealed flask at 120°C overnight. The resulting mixture was taken up into ice-cold HCl (6 N), which was extracted with EtOAc. The solution was concentrated and purified by flash column chromatography to give 1.6 g light brown solid (80%).

d) 6-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole

Following the procedure of Example 1(c) except for substituting 5-bromo-6-fluoro-3-methyl-1*H*-indazole for N-Boc-3-methyl-5-bromoindazole, the title compound was prepared.

e) [(1*S*)-2-[[5-(6-fluoro-3-methyl-1*H*-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f) except for substituting 6-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole for 3-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester in Example 1(b)-1(c) and substituting 3-furanylboronic acid for phenylboronic acid in Example 1(d)-1(e), the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.50(d, 1 H), 7.77(d, 2 H), 7.46-7.26(m, 8 H), 6.41(dd, 1 H), 4.42(dd, 1 H), 4.29(m, 1 H), 3.99(m, 1 H), 3.16(d, 2 H), 2.58(s, 3 H). MS (M+H): 443.2.

Example 105 Capsule Composition

An oral dosage form for administering the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table I, below.

Table I

INGREDIENTS	AMOUNTS
(S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 106 - Injectable Parenteral Composition

An injectable form for administering the present invention is produced by stirring 1.5% by weight of (S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine in 10% by volume propylene glycol in water.

Example 107 - Tablet Composition

The sucrose, calcium sulfate dihydrate and an Akt inhibitor as shown in Table II below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid;, screened and compressed into a tablet.

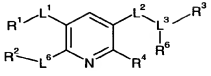
Table II

INGREDIENTS	AMOUNTS
(S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine	20 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A compound of Formula (I):



(I)

wherein:

L^1 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

L^2 is selected from the group consisting of a bond, -O-, heterocycle, -N(R^5)-, -N(R^5)C(O)-, -S-, -S(O)-, -S(O_2)-, and -C(O)N(R^5)-;

L^3 is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, methylamino, dimethylamino, oxo, and hydroxy;

L^6 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

R^1 is selected from the group consisting of aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocycle and substituted heterocycle;

R^2 is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, C_1-C_{12}aryl, aryloxy, substituted C_1-C_{12}aryloxy, -O(CH_2)$_q$$R^{31}$, -

NHC(O)-NHR^{41}, -C(O)R^{43}, substituted cycloalkyl, substituted C_1-C_{12}aryl, heterocycle, substituted heterocycle, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR^7, -C(O)NR^{8}R^9, -S(O)$_2$NR^{8}R^9, and -S(O)$_n$R^7,

where n is 0-2, q is 1-6,

R^7 is hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl,

R^{31} is C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, acyloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{41} is selected from hydrogen, C_1-C_{12}aryl, cycloalkyl and heterocycle, wherein C_1-C_{12}aryl, cycloalkyl and heterocycle are optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{43} is selected from C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl, and

R^8 and R^9 are independently hydrogen, cycloalkyl, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR^{10}, -S(O)$_n$R^{10}, -C(O)NR^{10}R^{11}, -S(O)$_2$NR^{10}R^{11}, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, and substituted aryl,

or R^8 and R^9 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^{10} and R^{11} are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2,

and when L^6 is a bond, R^2 can additionally be halogen;

R^3 and R^6 are independently selected from the group consisting of hydrogen, amino, methylamino, dimethylamino, aryl, substituted aryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, -S-C_1-C_{12}aryl, -O-C_1-C_{12}aryl, -OalkylC$_1$-C_{12}aryl, aryloxy, substituted aryloxy and arylalkoxy; and

R^4 is selected from the group consisting of hydrogen and halogen;

where R^5 is selected from the group consisting of hydrogen, -S(O)$_2$CH$_3$, -S(O)$_2$H and alkyl.

2. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of Formula (I), as described in claim 1.

3. The compound of Formula (I), as claimed in claim 1, wherein

L^1 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

L^2 is selected from the group consisting of a bond, -O-, heterocycle, -N(R^5)-, -N(R^5)C(O)-, -S-, -S(O)-, -S(O_2)-, and -C(O)N(R^5)-;

L^3 is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, methylamino, dimethylamino, oxo, and hydroxy;

L^6 is a bond;

R^1 is selected from the group consisting of C_1-C_{12}aryl and substituted C_1-C_{12}aryl;

R^2 is selected from alkyl, substituted alkyl, halogen, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, and C_1-C_{12}aryl optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, C_1-C_{12}aryl, C_1-C_{12}aryloxy, -O(CH$_2$)$_q$$R^{31}$, -NHC(O)-NHR^{41}, -C(O)R^{43}, hydroxy, alkoxy, cycloalkyl, N-acylamino, nitro and halogen,

where q is 1-6,

R^{31} is C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, acyloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{41} is selected from hydrogen, C_1-C_{12}aryl, cycloalkyl and heterocycle, wherein C_1-C_{12}aryl, cycloalkyl and heterocycle are optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{43} is selected from C_1-C_{12}aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxyl, nitro, tetrazole, cyano, oxo and trifluoromethyl,

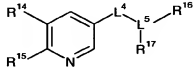
R^3 and R^6 are independently selected from the group consisting of hydrogen, amino, methylamino, dimethylamino, aryl, substituted aryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, -S-C_1-C_{12}aryl, aryloxy and arylalkoxy; and

R^4 is selected from the group consisting of hydrogen and halogen;

where R^5 is selected from the group consisting of hydrogen, -$S(O)_2CH_3$, -$S(O)_2H$ and alkyl.

4. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of Formula (I), as described in claim 3.

5. A compound of Claim 1 represented by the following Formula (II):



(II)

wherein:

L^4 is selected from the group consisting of a bond, heterocycle, and -O-;

L^5 is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from the group consisting of C_1-C_{12}aryl, and substituted C_1-C_{12}aryl;

R^{15} is selected from alkyl, substituted alkyl, halogen, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, C_1-C_{12}aryl and C_1-C_{12}aryl optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, aryloxy, $-O(CH_2)_qR^{31}$, -NHC(O)-NHR^{41}, -C(O)R^{43}, hydroxy, alkoxy, acyloxy, amino, cycloalkyl, N-acylamino, nitro, cyano and halogen,

where q is 1-6,

R^{31} is C_1-C_{12}aryl optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, and hydroxy,

R^{41} is selected from hydrogen and C_1-C_{12}aryl optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, and hydroxy,

R^{43} is C_1-C_{12}aryl substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, and hydroxy, and

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{12}aryl, substituted C_1-C_{12}aryl, heterocycle, cycloalkyl, -S-C_1-C_{12}aryl, and C_1-C_{12}arylalkoxy.

6. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of Formula (II), as described in claim 5.

7. A compound of Formula (II), as described in claim 5: wherein

L^4 is selected from the group consisting of a bond, and -O-;

L^5 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from the group consisting of C_1-C_{12}aryl, and substituted C_1-C_{12}aryl;

R^{15} is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{12}aryl and substituted C_1-C_{12}aryl.

8. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of Formula (II), as described in claim 7.

9. A compound of claim 1 selected from:

(S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-furan-2-yl-5-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[5,6-bis-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-thiophen-2yl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-(4-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-(3-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-benzyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclopent-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclopentyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclohex-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclohexyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

3-Methyl-5-[2-phenyl-5-(piperidin-4-ylmethoxy)-pyridin-3-yl]-1H-indazole;

3-[5-(3-Methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-propylamine;

(S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-thiophen-2-yl)-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-furan-2-yl)-pyridin-3-yloxy]-ethylamine;

3-Methyl-5-[2-phenyl-5-(4-pyridin-3-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole;

3-Methyl-5-[2-phenyl-5-(4-pyridin-4-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole;

[(1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(5-chloro-2-thienyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(3-aminophenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

(S)-1-Benzyl-2-[5-(1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-{6-[3-(3-fluoro-benzyloxy)phenyl]-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy}-ethylamine;

(S)-1-Benzyl-2-[5-(3-phenyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

N-{3-[5-{[(2S)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}benzamide;

N-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}-2,6-difluorobenzamide;

N-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}cyclohexanecarboxamide;

[(1*S*)-2-({5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(2-thienyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine;

[(1*S*)-2-({5-[3-(3-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(3-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

[(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(2-thienyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine;

[(1*S*)-2-({5-[3-(3-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(3-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

[(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1-methyl-1*H*-pyrazol-4-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-{1-[(3-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

((1*S*)-2-phenyl-1-{[(6-phenyl-5-{3-[5-(1-piperazinylmethyl)-2-furanyl]-1*H*-indazol-5-yl}-3-pyridinyl)oxy]methyl}ethyl)amine;

[(1*S*)-2-({6-(3-furanyl)-5-[3-(2-furanyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-(3-methyl-1*H*-indazol-5-yl)-6-[3-(phenyloxy)phenyl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

3-[({5-[5-(5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-2-phenyl-3-pyridinyl)-1*H*-indazol-3-yl]-2-furanyl}methyl)amino]propanenitrile;

[(1*S*)-2-({6-(2-furanyl)-5-[3-(2-furanyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

{5-[5-[[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]-2-thienyl}methanol;

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(phenylmethyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1-methyl-1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

5-(5-[[(2*S*)-2-amino-3-phenylpropyl]oxy}-2-phenyl-3-pyridinyl)-1*H*-indazol-3-amine;

[(1*S*)-2-({5-[3-(1-methylethenyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrazol-4-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

(2*S*)-*N*,*N*-dimethyl-1-{[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-3-phenyl-2-propanamine;

[(1*S*)-2-{[3-(3-methyl-1*H*-indazol-5-yl)-2,4'-bipyridin-5-yl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[3-(3-methyl-1*H*-indazol-5-yl)-2,3'-bipyridin-5-yl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-iodo-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-[(5-(3-methyl-1*H*-indazol-5-yl)-6-{3-[(trifluoromethyl)oxy]phenyl}-3-pyridinyl)oxy]-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(3,5-dimethyl-4-isoxazolyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

4-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

2-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

[(1*S*)-2-{[6-[3-(ethyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-(3-methyl-1*H*-indazol-5-yl)-6-[3-(methyloxy)phenyl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}(phenyl)methanone;

[(1*S*)-2-{[6-{3-[(1-methylethyl)oxy]phenyl}-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(2-{[(3-fluorophenyl)methyl]oxy}phenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(4-{[(3-fluorophenyl)methyl]oxy}phenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(5-chloro-2-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(4-methyl-2-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(5-methyl-2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(5-methyl-2-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-ethenyl-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(1*H*-pyrrol-2-yl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine;

[(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}methyl)ethyl]amine;

5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-*N*-(3-phenylpropyl)-3-pyridinamine;

5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-*N*-(3-phenylbutyl)-3-pyridinamine;

[(2*S*)-2-amino-3-phenylpropyl][5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine;

[(2*S*)-2-amino-3-phenylpropyl][6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]amine;

((1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-{[(phenylmethyl)oxy]methyl}ethyl)amine;

N-[(2*S*)-2-amino-3-phenylpropyl]-*N*-[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]methanesulfonamide;

5-(3-methyl-1*H*-indazol-5-yl)-*N*-[2-methyl-2-(phenylthio)propyl]-6-phenyl-3-pyridinamine;

[(1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(1*H*-indol-3-ylmethyl)ethyl]amine;

((1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-{[(phenylmethyl)oxy]methyl}ethyl)amine;

(2*S*)-2-amino-3-{[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-propanol;

5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-*N*-[(2*S*)-2-pyrrolidinylmethyl]-3-pyridinamine;

((2*S*)-2-amino-3-{4-[(phenylmethyl)oxy]phenyl}propyl)[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine;

[(2*S*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]amine;

[(2*S*)-2-amino-3-phenylpropyl][6-(3-furanyl)-5-(1*H*-indazol-5-yl)-3-pyridinyl]amine;

[(2*S*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-(3-thienyl)-3-pyridinyl]amine;

2-[5-{[(2*S*)-2-amino-3-phenylpropyl]amino}-3-(1*H*-indazol-5-yl)-2-pyridinyl]phenol;

2-[5-{[(2*S*)-2-amino-3-phenylpropyl]amino}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

[(2*S*)-2-amino-3-phenylpropyl][5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]amine;

[(2*S*)-2-amino-3-phenylpropyl][5-(3-methyl-1*H*-indazol-5-yl)-6-(5-methyl-2-thienyl)-3-pyridinyl]amine;

[(2*R*)-2-amino-3-phenylpropyl][5-(1*H*-indazol-5-yl)-6-(3-thienyl)-3-pyridinyl]amine;

2-[5-{[(2*S*)-2-amino-3-(1*H*-indol-3-yl)propyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol;

[(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}methyl)ethyl]amine;

[(1*S*)-2-(1*H*-indol-3-yl)-1-({[5-(3-methyl-1*H*-indazol-5-yl)-6-(5-methyl-2-thienyl)-3-pyridinyl]oxy}methyl)ethyl]amine;

[(1*S*)-2-{[6-ethyl-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(3-furanyl)-5-(1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-ethenyl-1*H*-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-ethyl-1*H*-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({6-(3-furanyl)-5-[3-(3-pyridinyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-methyl-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-(3-methyl-1*H*-indazol-5-yl)-6-[2-(methyloxy)phenyl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-[2-(ethyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-[5-chloro-2-(methyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-[5-fluoro-2-(propyloxy)phenyl]-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(1-methylethyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine; and

[(1*S*)-2-{[5-(6-fluoro-3-methyl-1*H*-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine.

10. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of Formula (II), as described in claim 9.

11. A pharmaceutical composition comprising a compound according to claim 1, and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof and a pharmaceutically acceptable carrier.

12. A process for preparing a pharmaceutical composition containing a pharmaceutically acceptable carrier or diluent and an effective amount of a compound of Formula (I) as described in claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof, which process comprises bringing the compound of Formula (I) and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof into association with a pharmaceutically acceptable carrier or diluent.

13. A method of treating or lessening the severity of a disease or condition selected from cancer and arthritis in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of Formula I, as described in claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof.

14. The method of claim 13 wherein the mammal is a human.

15. A method of treating or lessening the severity of a disease or condition selected from cancer and arthritis in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of Formula II, as described in claim 5 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof.

16. The method of claim 15 wherein the mammal is a human.

17. The method according to claim 13 wherein said cancer is selected from brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

18. The method according to claim 15 wherein said cancer is selected from brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

19. Use of a compound of Formula (I), as described in claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof, in the manufacture of a medicament for use in treating or lessening the severity of a disease or condition selected from cancer and arthritis.

20. The method of inhibiting Akt activity in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of Formula I, as described in claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof.

21. The method of claim 20 wherein the mammal is a human.

22. A method of treating cancer in a mammal in need thereof, which comprises: administering to such mammal a therapeutically effective amount of

a) a compound of Formula (I), as described in claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof; and

b) at least one anti-neoplastic agent.

23. The method claim 22, wherein the at least one anti-neoplastic agent is selected from the group consisting essentially of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

24. The method of claim 22, wherein the at least one anti-neoplastic agent is an anti-microtubule agent selected from diterpenoids and vinca alkaloids.

25. The method of claim 22, wherein the at least one anti-neoplastic agent is a diterpenoid.

26. The method of claim 22, wherein the at least one anti-neoplastic agent is a vinca alkaloid.

27. The method of claim 22, wherein the at least one anti-neoplastic agent is a platinum coordination complex.

28. The method of claim 22, wherein the at least one anti-neoplastic agent is paclitaxel, carboplatin, or vinorelbine.

29. The method of claim 22, wherein the at least one anti-neoplastic agent is paclitaxel.

30. The method of claim 22, wherein the at least one anti-neoplastic agent is carboplatin.

31. The method of claim 22, wherein the at least one anti-neoplastic agent is vinorelbine.

32. The method of claim 22, wherein the at least one anti-neoplatic agent is a signal transduction pathway inhibitor.

33. The method of claim 32, wherein the signal transduction pathway inhibitor is an inhibitor of a growth factor receptor kinase selected from the group consisting of VEGFR2, TIE2, PDGFR, BTK, IGFR-1, TrkA, TrkB, TrkC, and c-fms.

34. The method of claim 32, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of rafk, akt, and PKC-zeta.

35. The method of claim 32, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the src family of kinases.

36. The method of claim 35, wherein the signal transduction pathway inhibitor is an inhibitor of c-src.

37. The method of claim 32, wherein the signal transduction pathway inhibitor is an inhibitor of Ras oncogene selected from inhibitors of farnesyl transferase and geranylgeranyl transferase.

38. The method of claim 32, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K.

39. The method of claim 22, wherein the at least one anti-neoplastic agent is a cell cycle signaling inhibitor.

40. The method of claim 39, wherein the cell cycle signaling inhibitor is selected from inhibitors of the group CDK2, CDK4, and CDK6.

41. A pharmaceutical combination as claimed in claim 22 for use in therapy.

42. The use of a pharmaceutical combination as claimed in claim 22 for the preparation of a medicament useful in the treatment of cancer.

ABSTRACT OF THE DISCLOSURE

Invented are novel pyridine compounds, the use of such compounds as inhibitors of PKB/AKT kinase activity and in the treatment of cancer and arthritis.